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THE CLINICAL SIGNIFICANCE OF THE PATHOLOGICAL CHANGES IN HODGKIN'S DISEASE. By DOUGLAS SYMMERS, M.D. 157

TUBERCULOSIS AS AN ETIOLOGICAL FACTOR IN HODGKIN'S DISEASE: A HISTORICAL REVIEW. By WILLIS S. LEMON, M.B. (TOR.) 178

MANAGEMENT OF THE DIABETIC PATIENT, WITH ESPECIAL REFERENCE TO THE ADMINISTRATION OF INSULIN. By WILLARD C. STONER, M.D. 189

PERFORATION OF THE ESOPHAGUS DUE TO INSTRUMENTATION (WITH A REPORT OF THREE CASES). By JULIUS FRIEDENWALD, M.D., and THEODORE H. MORRISON, M.D. 194

A DISCUSSION OF THE ETIOLOGY OF ASTHMA IN ITS RELATIONSHIP TO THE VARIOUS SYSTEMS COMPOSING THE PULMONARY NEUROCELLULAR MECHANISM WITH THE PHYSIOLOGICAL BASIS FOR THE EMPLOYMENT OF CALCIUM IN ITS TREATMENT. By F. M. POTTENGER, M.D. 203

A CASE OF ACQUIRED CHRONIC HEMOLYTIC (ACHOLURIC) JAUNDICE, SEEN FIFTEEN YEARS AGO WITH A BLOOD-PICTURE AT THAT TIME RESEMBLING ONE OF PERNICIOUS ANEMIA. By F. PARKES WEBER, M.A., M.D., F.R.C.P. 220

THE DIAGNOSIS AND MANAGEMENT OF SUPRAVESICAL HEMATURIAS. By PAUL W. ASCHNER, M.D. 225

UNCOMPLICATED DISLOCATIONS OF THE SHOULDER: THEIR RATIONAL TREATMENT AND LATE RESULTS. By KARL SCHLAEPFER, M.D. 244

REPORT OF SIX CASES OF CUTANEOUS ANTHRAX TREATED BY THE LOCAL AND GENERAL ADMINISTRATION OF ANTI-ANTHRAX SERUM. By JOSEPH C. REGAN, M.D., and CATHERINE REGAN, M.D. 255

SYPHILIS OF THE HEART AND BLOODVESSELS. By TASKER HOWARD, M.D. . . . 266

RHEUMATOID ARTHRITIS, WITH REMARKS ON THE USE OF COLEY'S TOXIN IN THE TREATMENT OF THIS CONDITION. By ROBERT TORREY, M.D., and THOMAS KLEIN, M.D. 275

INDEX TO ADVERTISERS . . . . . ADV. PAGE 35

Contents continued on page x

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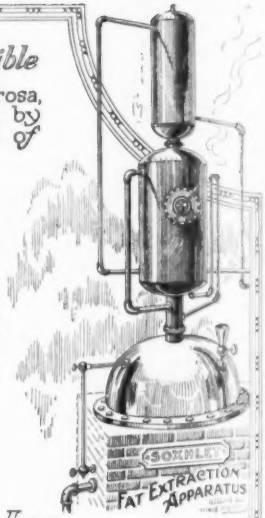

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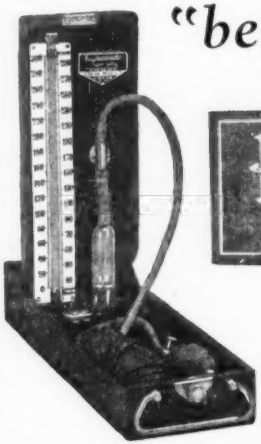

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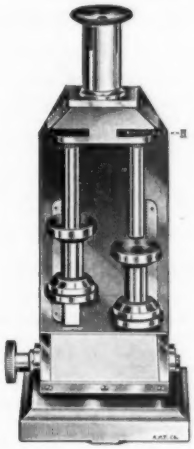

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CONTENTS

ORIGINAL ARTICLES

The Clinical Significance of the Pathological Changes in Hodgkin's Disease 157
By Douglas Symmers, M.D., New York.

Tuberculosis as an Etiological Factor in Hodgkin's Disease: A Historical Review 178
By Willis S. Lemon, M.B., (Tor.), Rochester, Minn.

Management of the Diabetic Patient, With Especial Reference to the Administration of Insulin 189
By Willard C. Stoner, M.D., Cleveland, Ohio.

Perforation of the Esophagus Due to Instrumentation (With a Report of Three Cases) 194
By Julius Friedenwald, M.D., and Theodore H. Morrison, M.D., Baltimore.

A Discussion of the Etiology of Asthma in its Relationship to the Various Systems Composing the Pulmonary Neurocellular Mechanism with the Physiological Basis for the Employment of Calcium in its Treatment 203
By F. M. Pottenger, M.D., Monrovia, Calif.

A Case of Acquired Chronic Hemolytic (Acholuric) Jaundice, Seen Fifteen Years ago with a Blood-picture at that Time Resembling One of Pernicious Anemia 220
By F. Parkes Weber, M.A., M.D., F.R.C.P., London, England.

The Diagnosis and Management of Supravesical Hematurias 225
By Paul W. Aschner, M.D., New York.

Uncomplicated Dislocations of the Shoulder: Their Rational Treatment and Late Results 244
By Karl Schlaepfer, M.D., New Haven, Conn.

Report of Six Cases of Cutaneous Anthrax Treated by the Local and General Administration of Anti-anthrax Serum 255
By Joseph C. Regan, M.D., and Catherine Regan, M.D., New York.

Syphilis of the Heart and Bloodvessels 266
By Tasker Howard, M.D., Brooklyn, N. Y.

Rheumatoid Arthritis, With Remarks on the Use of Coley's Toxin in the Treatment of This Condition 275
By Robert Torrey, M.D., and Thomas Klein, M.D., Philadelphia.

(*Contents continued on page 12*)

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REVIEWS

The Treatment of Diabetes Mellitus. By Elliott P. Joslin, M.D. . . . 283
Applied Anatomy and Kinesiology. By Wilbur Pardon Bowen, M.S. . . 284
Individual Gymnastics. By Lillian Curtis Drew 284
The Fundamentals of Bacteriology. By Charles Bradfield Morrey, B.A., M.D. 285
Arboreal Life and the Evolution of the Human Eye. By E. Treacher Collins, F.R.C.S. 285
The Physiology of Twinning. By H. H. Newman 285
Protists and Disease. By J. Jackson Clarke, F.R.S.C. 286
Rhus Dermatitis. By James B. McNair, M.D. 286
A Text-book of Chemistry for Nurses. By Fredus N. Peters, A.M., Ph.D. 287
Obstetrics for Nurses. By Charles B. Reed, M.D. 287
Discours de la Nature de l'Air; de la Vegetations des Plantes. By Edme Mariotte 288
The Action of Alcohol on Man. By Ernest H. Starling 288
The New Dietetics. By John Harvey Kellogg, M.D., LL.D., F.A.C.S . 289
Diagnostic Methods. By Herbert Thomas Brooks, A.B., M.D., F.A.C.P. 289
Infection, Immunity and Biologic Therapy. By John A. Kolmer, M.D. 290

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D., AND ROGER S. MORRIS, M.D.

Intravascular Injection of Iodized Oil 291
Sickle-cell Anemia 292
A Warning Against the Use of Arsphenamine in the Treatment of Syphilis in a Hemophiliac 292
Spinal Subarachnoid Block 293
The Size of the Heart in Pneumonia 293
The Treatment of Syphilis with Bismuth 293

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.

Further Observations on the Blood-pressure in Cases of Urinary Obstruction 294
Operations for Inguinal Hernia Under Local Anesthesia 294
Vasostomy for Seminal Vesiculitis 295
Secondary Signs of Gall-bladder Pathology 295
A Conservative Treatment of Carbuncles 295
The Surgical Management of Gall-bladder Disease 296

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.

Medical Methods of Controlling Hemorrhage 297
The Treatment of Vincent's Angina with Trypaflavin 297
Studies of Turpentine 297
The Effect of Alkalis on Gastric Secretion and Motility as Measured by Fractional Gastric Analysis 298
The Pathogenicity and Treatment of Flagellate Dysentery 298

(*Contents continued on page 14*)

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Acidified Whole Milk as a Routine Infant Food 299
Recurring Cardiac Infections in Children with Chronic Valvular Disease 300
Chronic Ulcerative Colitis in Childhood 300
Relative Immunity of Infants under Five Months of Age to Infection with Measles 301

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.

Marital Syphilis 302
Acute Disseminate Erythematous Lupus 302
Arsphenamine in Treatment of Syphilis 303
Treatment of Dermatitis Venenata 303

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.

The Treatment of Patients Pregnant and Tuberculous 303
Vasomotor Tone During Pregnancy 304
Hydatidiform Mole and Chorioepithelioma 305

(*Contents continued on page 16*)

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CONTENTS—(*Continued*)

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D., AND FRANK B. BLOCK, M.D.

Intracervical Enucleation 306
Value of Cervical Surgery 307
Hysteropexy for Prolapse of the Uterus 307

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M., AND DE WAYNE G. RICHEY, B.S., M.D.

The Complement-fixation Reaction as Applied to Leprosy 308
A Study of Rabbit Spirochetosis 309

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D., AND GEORGE W. McCOY, M.D.

Studies on Pneumococcus Immunity. II. Active Immunization of Monkeys with the Homologous Pneumococcus Vaccine 310
Schick Tests and Immunization Against Diphtheria in the Eighth Sanitary District of Vermont 310
Changes in a Small Town Brought About by the Health Department . 311
A Bacteriological Study of Vulvovaginitis of Children 311
Further Notes upon Experimental Measles in Rabbits and Monkeys . . 312
The Devil's Grip in Virginia 312
Does Commercial Pasteurization Destroy Tubercle Bacilli in Milk . . 312

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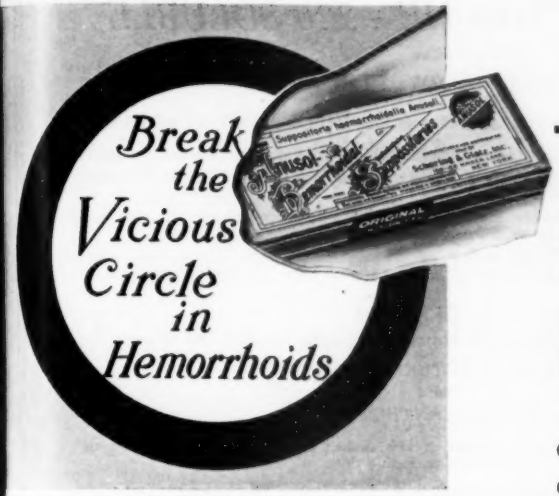

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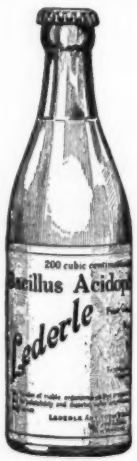

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ORIGINAL ARTICLES.

THE CLINICAL SIGNIFICANCE OF THE PATHOLOGICAL CHANGES IN HODGKIN'S DISEASE.

By Douglas Symmers, M.D.,

DIRECTOR OF LABORATORIES, BELLEVUE AND ALLIED HOSPITALS, NEW YORK.

(From the Pathological Laboratories of Bellevue Hospital.)

In 1832 Hodgkin called attention to a disease characterized by progressive enlargement of the lymph nodes associated with enlargement of the spleen.[1] Five of the 7 cases originally described by him were undoubtedly types of lymph-node tuberculosis or syphilis, or of leukemia, lymphosarcoma or pseudoleukemia, but the remaining 2 were almost certainly genuine examples of the affection to which Wilks,[2] in 1856, gave the name of Hodgkin's disease. Over a space of nearly seventy years after the appearance of Hodgkin's paper innumerable contributions were made to the subject, and Hodgkin's disease came to represent an apparently hopeless conglomeration of lymph-node and splenic enlargements. In 1899, however, Sternberg[3] established the fact that Hodgkin's disease is a histological entity, the changes in the lymph nodes and elsewhere consisting in the appearance of a connective-tissue reticulum supporting variable numbers of lymphocytes, together with mononuclear and multinuclear giant cells, with or without an admixture of eosinophiles. This histological composite is now generally accepted as the criterion on which the diagnosis of Hodgkin's disease is to be made.

During the past fifteen years 14 cases of Hodgkin's disease have been encountered in the pathological laboratories of Bellevue

Hospital among 8485 autopsies. These cases have been made the subject of clinical, anatomical and histological studies, and form the basis of the present communication. From the pathological viewpoint they are divisible into two groups and are so arranged in this paper. In the first group are included those cases in which the characteristic histological changes are limited to the lymphoid tissues, that is to say, to the lymph nodes proper and to the lymphoid follicles in the spleen and in the walls of the portal vessels and to other residual foci in the lungs, bone-marrow, kidney, adrenal, subcutaneous tissues, serous membranes, etc. In the second group are included those cases in which, in addition to changes of the same sort and in the same localities, the disease mechanically infiltrates skeletal muscles, bloodvessels, serous membranes and loose tissues, and, by direct pressure, erodes bone or partially replaces viscera.

In preparing these cases for publication irrelevant detail has been omitted, and only those facts are offered for consideration which appeared to be of value in the present connection. This presentation comprises, among other things: (1) A series of cases in which the pathological changes were confined to the lymphoid system, including (*a*) a newly recognized variety of Hodgkin's disease of the liver, (*b*) a discussion of Hodgkin's disease of the spleen as a clinical and pathological entity, and (*c*) an example of Hodgkin's disease associated with changes in the skin resembling the so-called acanthosis nigricans; (2) a series of cases showing invasive destruction of the skeletal muscles; (3) a discussion of Hodgkin's disease of the thymic remains attended by invasion and destruction of neighboring tissues; (4) an analysis of the lymph-node changes, with particular reference to the rarity of massive Hodgkin's disease of the cervical nodes and the frequency of predominant abdominal, or of predominant combined abdominal and thoracic involvement; (5) a discussion of the changes in the several viscera; (6) a theory of the histogenesis of Hodgkin's disease as an affection of the hemolytopoietic system; (7) a consideration of the apparent kinship of the disease to chronic myelogenous leukemia; (8) a discussion of the nature of Hodgkin's disease—whether inflammatory or neoplasmic; (9) a résumé of its symptoms and signs, duration, treatment, etc.

CASE I. **Group I. Changes Confined to Lymphoid Tissues.**—H. M., a school-girl, aged sixteen years, was admitted to Bellevue Hospital, October 28, 1919; died January 7, 1920. She stated that three years previously she had noticed a swelling on the left side of the neck that was about the size of a cherry. The growth was painless and continued to enlarge to such an extent that within five months it had attained the size of a small orange. Two years later the patient noticed a small swelling on the right side of the

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neck, apparently of the same nature as that on the left. In the winter of 1918 she was afflicted by the prevailing pandemic pneumonia. During that time the nodes in the neck disappeared almost completely. Shortly thereafter, however, they again enlarged and increased rapidly in size, those on the right side attaining greater proportions than those on the left. In the course of the next six months the cervical nodes received ten roentgen-ray exposures at the hands of an extramural physician. The patient was now very weak, short of breath and suffered from a productive cough.

Physical examination showed, among other things, enormous enlargement of the supraclavicular lymph nodes, together with those of the submaxillary region, the anterior and posterior cervical nodes and the nodes of the right axilla. The neck measurements at the upper level showed a circumference of 42.5 cm., 46 cm. at the center and 52 cm. at the base. Early in January the patient's cough became so distressing as to interfere with sleep, and she complained of difficulty in swallowing. Three days later the skin and conjunctivæ assumed a faint icteroid tint, which gradually deepened until the time of death. The inguinal nodes were not enlarged. The red cells numbered 2,300,000; hemoglobin, 35 per cent; white cells, 7000; polymorphonuclear neutrophiles, 76 per cent; lymphocytes, 20 per cent; large mononuclear cells, 2 per cent; transitionals, 2 per cent. A superficial lymph node was excised and the pathological diagnosis was made of Hodgkin's disease.

Duration of symptoms: Three years and two months.

Autopsy Findings. Hodgkin's disease, with massive enlargement of the cervical lymph nodes and of the lymph nodes at the superior aperture of the thorax; extensive hyperplasia of the periaortic and peripancreatic nodes and those at the hilus of the liver; solitary nodule in the neck of the gall-bladder and in the mucosa of the left bronchus; slight enlargement of peribronchial lymph nodes; splenomegaly with innumerable nodular foci; multiple nodules in liver.

Histology. Microscopical examination of enlarged lymph nodes from the neck showed a fine connective-tissue reticulum, imbedded in which were comparatively small numbers of lymphocytes, numerous eosinophiles, moderate numbers of large mononuclear cells and a profusion of multinuclear giant cells of the myeloid type. In addition there were numerous wide, streak-like or intercommunicating necrotic foci, many of which were infiltrated by small, poorly chromatic cells of the fibroblastic type resting in a stroma of indefinite composition. The smaller bloodvessels in or near the necrotic areas were partially or completely obliterated as a result of heaping up of the lining endothelium and thickening of the walls. The microscopical changes in the spleen were essen-

tially identical with those in the lymph nodes. The liver showed numerous large and small collections of cells lying in the periportal spaces that were composed of a reticulum supporting prominent numbers of eosinophiles and eosinophilic myelocytes, lymphocytes and mononuclear and multinuclear giant cells. Smears from the marrow of the sternum showed numbers of well-preserved red corpuscles, numerous normoblasts, many neutrophilic myelocytes, a few eosinophilic myelocytes, eosinophiles, large mononuclear cells and myeloblasts. Sections from the marrow were richly cellular, showing large numbers of multinuclear giant cells. In places the marrow was permeated by fibroblasts.

Comment. This case affords an example of the readiness with which the structures of the neck and thorax, notably the trachea and bronchi and the esophagus, are able to adapt themselves to gradually increasing pressure for a long period of time before giving rise to symptoms, as shown by the fact that the patient did not complain of pressure disturbances until after the lapse of at least two years of widespread lymph-node involvement in the neck and thorax. Moreover, in spite of compression of the structures of the portal space by masses of enlarged lymph nodes, the biliary drainage system was able to function for a long period in such efficient fashion that obstructive changes occurred only as a terminal event. The case is also noteworthy as illustrating the almost complete disappearance of the enlarged lymph nodes in the neck after a siege of infection, followed by progression when the infection had subsided.

The histological changes in the cervical lymph nodes and elsewhere permit of several deductions of practical value, particularly in view of the fact that the cervical nodes had been subjected to roentgen-ray therapy and were the seat of necrotic foci, attended by obliteration of the smaller bloodvessels, followed by an attempt to substitute the dead areas by connective tissue. These changes are comparable to those which, it is claimed, occur in certain malignant growths after roentgen-ray therapy. In the case under consideration, however, histological alterations identical with those in the lymph nodes of the neck, which had been subjected to radiation, were also found in the spleen and in the enlarged lymph node in the wall of the gall-bladder, neither of which had been exposed to the roentgen-ray. Moreover, identical necrotic and replacement changes were observed in the lymph nodes and spleen in other cases of this series where the roentgen-ray had not been employed at all.

This is the only case of massive Hodgkin's disease of the cervical lymph nodes to be encountered in this series.

CASE II.—The patient, J. W., aged sixty-six years, was admitted to Bellevue Hospital on October 7, 1916, complaining of pain in

the left side of the abdomen, swelling of the feet and cough. He stated that in October of the previous year he had entered another hospital because of enlarged lymph nodes on the right side of the neck; the opposite side was not affected. While in the hospital one of the enlarged lymph nodes was removed and a diagnosis of Hodgkin's disease was made. Soon after leaving the hospital the swelling of the neck increased, and he began to have sharp pains in the abdomen to the left of the umbilicus. This pain, in time, became continuous and interfered with sleep. Just before entering Bellevue Hospital the patient noticed that his feet were swollen.

At the time of admission to Bellevue Hospital physical examination showed that there were lymph nodes on the right side of the neck that combined to form a large mass. A few enlarged lymph nodes were likewise present on the left side of the neck and in the right axilla and in both inguinal regions. The abdomen was distended by fluid. The spleen was palpated 8 cm. below the costal margin in the left anterior axillary line and was tender. The liver was not felt. Five days after entering Bellevue Hospital the patient died of croupous pneumonia. At the time of admission the white cells numbered 18,000, of which there were 94.5 per cent polymorphonuclear neutrophiles, 2.5 per cent lymphocytes, 1.5 per cent large mononuclear cells and 1.5 per cent transitionals.

Duration of symptoms: One year and three months.

Autopsy Findings. Hodgkin's disease affecting the nodes of the right side of the neck, right axillary and both inguinal regions and peripancreatic, periaortic and iliac groups; extensive replacement of vertebræ; multiple nodules in liver and spleen; minute nodules in both kidneys; ascites.

Histology. The most striking feature in the histology of the lymph nodes removed from various parts of the body and of the spleen was to be found in the pronounced overgrowth of connective tissue, which in places was mature, in other places rather richly fibroblastic. In the connective tissues, arranged diffusely or as islands or streak-like areas, were lymphoid cells, relatively large numbers of large mononuclear cells and a liberal sprinkling of multinuclear giant cells; eosinophiles were scarce. In the periportal tissues were large collections of cells of identical composition. Preparations from the vertebræ showed different histological changes in the same section. In places the marrow spaces were filled by tissue of the same sort as that encountered in the lymph nodes and elsewhere. In other places the marrow spaces were occupied by granulation tissue, in which were eosinophiles and eosinophilic myelocytes, large mononuclear cells and polymorphonuclear neutrophiles. In such areas myeloid giant cells were conspicuous by their absence. In still other parts the bone-marrow was rich in cells of the lymphocytic and plasma type, together with large mononuclear and multinuclear giant cells, eosinophiles

and eosinophilic myelocytes, representing, apparently, hyperplasia of cells normally encountered in the marrow.

Comment. This case represents one of combined cervical and abdominal Hodgkin's disease without participation of the thoracic nodes, together with foci in the liver and kidney, a markedly enlarged and sclerotic spleen and extensive invasion of the vertebral column.

CASE III.—T. F., a Greek laborer, aged twenty years, was admitted to Bellevue Hospital, January 25, 1917, and died March 3, the same year. The patient complained chiefly of dyspnea of a month's duration. He stated that six months previous to admission he had noticed swelling of the ankles, followed a short time thereafter by enlargement of the inguinal lymph nodes on both sides.

Physical Examination. The inguinal lymph nodes on both sides and the nodes of the femoral chain on the right side were enlarged. Within a month after admission the patient became generally edematous and the abdomen was distended by fluid. A month before death a few slightly enlarged lymph nodes appeared in the cervical region. The blood count revealed 3,800,000 red cells; 2200 white cells, of which 85 per cent were polymorphonuclear neutrophiles, 10 per cent lymphocytes, 2 per cent large mononuclears and 3 per cent transitionals. Microscopical examination of sections made from an excised inguinal lymph node showed the histology of Hodgkin's disease with numbers of mononuclear and multinuclear giant cells.

Duration of symptoms: Approximately seven months.

Autopsy Findings. Hodgkin's disease of abdominal and inguinal lymph nodes with slight involvement of the cervical nodes; nodules in the spleen and liver, in the parietal and frontal bones and in the posterior urethra; edema of lower extremities due to compression of iliac veins by enlarged lymph nodes; bilateral hydrothorax; ascites; emaciation; exfoliative dermatitis; suppurating surgical incisions in both groins; secondary suppurative lymphadenitis of abdominal lymph nodes.

Histology. Enlarged lymph nodes from different localities and sections from the spleen, ileum and appendix showed the characteristic changes of Hodgkin's disease—a reticulated stroma supporting lymphocytes, large mononuclear and multinuclear giant cells and a few eosinophiles. Sections from the bone-marrow showed lymphocytic and plasma cells in abundance, eosinophiles and eosinophilic myelocytes and typical mononuclear giant cells, together with an occasional multinuclear giant cell, the morphology of which was indistinguishable from those normally encountered in the marrow. The vast majority of the giant cells, however, were atypical, that is to say, their nuclei were extremely dense

and deeply staining and assumed all sorts of odd shapes—irregularly rounded or oval or semilunar, rectangular or dumbbell-shaped, jagged or stellate—the cytoplasm staining faintly pinkish. On account of the presence of large numbers of polymorphonuclear neutrophiles in the other tissues, particularly in the enlarged lymph nodes, it was impossible to identify atypical giant cells in sections. In the liver, however, microscopical examination of the nodular foci showed a connective-tissue stroma supporting large numbers of mononuclear cells and a fairly rich sprinkling of multinuclear giant cells and, among the latter, atypical forms, corresponding to those met with in the bone-marrow, were to be seen, the nodules in the liver presenting only a few polymorphonuclear neutrophiles to obscure the histological picture of Hodgkin's disease.

Comment. In this case correlation of the clinical and anatomical findings points to the conclusion that the first clinically detectable signs of disease were dependent on enlargement of the abdominal lymph nodes, as shown by edema of the lower extremities followed by enlargement of the inguinal nodes. The cervical nodes were involved late and then only to a negligible extent, while the thoracic nodes escaped. Another feature of interest is to be found in the occurrence of atypical multinuclear giant cells in the bone-marrow and the identification of similar cells in the nodules in the liver, as indicating that the cells in the liver were derived from the bone-marrow by the process of embolism.

Finally, it is to be observed that the patient died as a result of secondary infection following the removal of enlarged inguinal lymph nodes for purposes of diagnosis. In this connection it is to be recalled that surgical wounds of the groin are apt to become infected easily, sometimes even though the utmost care be exercised, as, for example, in hernia operations, and that such infections are difficult to control. In Hodgkin's disease removal of the inguinal lymph nodes for diagnosis is, in my opinion, a procedure to be undertaken only in extraordinary circumstances, and then at the hands of a surgeon who is prepared to exercise every precaution against infection. It is not an operation to be entrusted to the casual.

CASE IV.—J. S., male, aged forty-seven years, was admitted to Bellevue Hospital, March 23, 1917, and died April 4, the same year.

Physical examination revealed slight cyanosis, particularly of the extremities. There were signs of fluid at the bases of both lungs. The superficial veins of the abdominal wall were dilated, the abdomen was distended and there was shifting dulness in both flanks. Paracentesis released 2000 cc of yellow cloudy fluid from the left chest. On March 3, 1500 cc of fluid were removed from the abdomen, after which the liver and spleen were easily palpated.

There was a large mass of lymph nodes in the left groin and a similar, but smaller, collection on the right side. Enlarged lymph nodes were palpated in both axillæ, but the cervical region was free. The white cells numbered 13,200; polymorphonuclear neutrophiles, 92 per cent; small lymphocytes, 5 per cent; large mononuclears, 2 per cent; transitionals, 1 per cent.

Duration of symptoms: Doubtful.

Autopsy Findings. Hodgkin's disease of the abdominal and thoracic lymph nodes with relatively slight involvement of the axillary and inguinal groups; splenomegaly; nodules in liver and in cortices of kidneys; involvement of bone-marrow; ascites; hydrothorax.

Histology. The lymph nodes and spleen, the perilobular spaces of the liver and the bone-marrow showed a fibroblastic connective-tissue reticulum, scattered through which were relatively small numbers of lymphoid cells and numerous eosinophiles and eosinophilic myelocytes, arranged diffusely or in groups, and variable numbers of large mononuclear cells and myeloid giant cells.

Comment. This case is one of predominant involvement of the abdominal nodes, with associated enlargement of the peribronchial lymph nodes, without, however, any indication of participation of the nodes in the neck.

CASE V.—The patient, M. B., female, aged twelve years, was admitted to Bellevue Hospital on December 29, 1921, and died February 6, 1922. Her mother stated that six years previously she had noticed a small mass on the right side of the child's neck and that the patient vomited frequently. She took the child to the Kings County Hospital in Brooklyn, where an enlarged node was excised and, according to the mother, was reported as Hodgkin's disease. Subsequently the patient suffered a number of attacks characterized by weakness, anorexia, vomiting and pain in the upper part of the abdomen. During several of these attacks she was jaundiced. Six weeks before admission to Bellevue Hospital, the patient suffered an attack attended by jaundice and by pains in the abdomen of such severity that she fainted on several occasions.

Physical Examination. An emaciated and jaundiced girl, in whom the liver and spleen were palpable. The skin presented signs of bran-like desquamation. At the angle of the jaw on the right side was a nodular mass, about 2 cm. in length. A few similar nodules were present in the front of the neck on the right side. The roentgen-ray report was to the effect that there were enlarged lymph nodes at the root of both lungs. The blood count revealed 2,568,000 red cells, 60 per cent hemoglobin and 6700 white cells, of which 69 per cent were polymorphonuclear neutrophiles, 24 per cent lymphocytes and 7 per cent eosinophiles.

Duration of symptoms: Six years and one month.

Autopsy Findings. Hodgkin's disease with massive enlargement of the abdominal lymph nodes and extensive changes in the nodes of the thorax; slight enlargement of nodes of neck; splenomegaly; obstructive jaundice; chronic passive congestion of liver with multiple nodular foci; generalized exfoliative dermatitis.

Histology. Microscopical examination of lymph nodes removed from different parts of the body showed the presence of irregular but widespread overgrowth of rather poorly cellular fibrous tissue. In some of the nodes the architecture was altered to such an extent that the histological diagnosis of Hodgkin's disease could be made, if at all, only with difficulty. Other lymph nodes were extensively but irregularly replaced by sclerotic connective tissue supporting relatively scanty numbers of lymphocytes, among which large mononuclear cells were scattered in fair abundance, together with an occasional giant cell of the myeloid type. Eosinophiles could not be seen. The spleen likewise showed extensive replacement by connective tissue, particularly in the region of the Malpighian follicles, the vessels of which were practically always occluded or their lumina reduced to a minimum, the lymphoid remains, if any, lying in thick bundles or streaks of plaque-like, hyalinized connective tissue. In the spleen giant cells could not be detected. For the greater part, the perilobular tissues in the liver were occupied by rounded, oval or streak-like collections of lymphocytes with a few mononuclear giant cells and, rarely, a giant cell of the myeloid type.

Comment. This case is one of a young girl who, for a period of slightly more than six years suffered from attacks characterized by nausea, vomiting and pain in the upper abdomen, attended by several attacks of jaundice. Anatomically, the disease was marked by enormous enlargement of the abdominal lymph nodes. Nodes which compressed the structures at the hilus of the liver accounted for the jaundice. The peribronchial lymph nodes were enlarged, although to a less extent than those in the abdomen, and the nodes of the neck were only slightly involved. The patient complained of no symptoms referable to the chest with the exception of a cough of short duration. The most striking feature in the histological examination consisted in the widespread overgrowth of connective tissue in certain of the lymph nodes and in the spleen. In the latter locality, it was particularly noticeable, occurring to such an extent as to obscure the characteristic histology of Hodgkin's disease.

CASE VI.—The patient, a man, aged thirty-nine years, was admitted to Bellevue Hospital for the second time on August 10, 1916, and died April 18, 1917. He stated that three years previously he had observed small nodules in the neck and axilla and that in the course of the next year, these increased to such an extent that he submitted to a surgical operation for their removal.

He first came to Bellevue Hospital, in 1915, because of recurrence of the growths, and a small nodule was removed for diagnosis. At the time of the patient's re-admission to Bellevue Hospital, in 1916, he complained of pains in the back and of intervals of diarrhea alternating with constipation. The spleen was palpable 7½ cm. below the left costal margin and the liver 5 cm. below the costal margin on the right side. In the right upper quadrant of the abdomen was a large, firm mass, lying to the right of the umbilical region, and there were slightly enlarged nodes in the neck and axillary and inguinal regions. There were no signs of fluid to be detected in the abdomen, but the scrotum was markedly edematous. In the interval between March 31 and April 10, 1917, the patient's spleen and the enlarged nodes in the neck were subjected to roentgen-ray exposures, after which the spleen is said to have diminished in size by about 5 cm., as measured by palpation.

Duration of symptoms: Three years and eight months.

Autopsy Findings. Hodgkin's disease, with massive enlargement of the abdominal lymph nodes; moderate hyperplasia of the mediastinal and peribronchial nodes; splenomegaly; multiple nodular foci in liver.

Histology. Microscopical examination of the lymph node removed from the neck in 1915 showed a thickened and hyalinized capsule from which trabeculæ penetrated downward for variable distances. In the intervals between the trabeculæ were collections of lymphoid cells, a few large mononuclear cells and an occasional giant cell of the myeloid type. Eosinophiles were not noted. In certain of the lymph nodes removed at autopsy the degree of connective-tissue replacement was even more pronounced than in the node excised during life; the lymphoid cells were visible only as minute islands widely separated by masses of hyalinized fibrous tissue, the architecture of the nodes being so altered that the diagnosis of Hodgkin's disease could not be made on the basis of histological appearances. In other words, the microscopical changes in lymph nodes removed, respectively, three years before radiation and two weeks after radiation, showed changes which were qualitatively identical. Microscopical examination of the spleen, which had several times been exposed to radiation during a period of two weeks immediately before death, showed widespread replacement of the normal architecture by streak-like bands of cellular, well-fibrillated connective tissue, between which were large collections of lymphoid cells and numbers of mononuclear and multinuclear giant cells. The smaller bloodvessels in the spleen, almost without exception, showed heaping-up of the lining endothelium, thickening of the walls and diminution or occlusion of the lumina. It was obvious that the fibrotic and vascular changes were of such maturity as to eliminate any possible relationship to the roentgen-ray exposures that had been made in the last few weeks of life.

In the perilobular spaces of the liver were large and small collections of cells consisting of a delicate reticulum, likewise enclosing lymphocytes and mononuclear and multinuclear giant cells. Among the latter were many with atypical nuclei.

CASE VII.—F. R., male, aged forty-eight years, was admitted to Bellevue Hospital, September 22, 1915, and died December 12, 1915. His complaint consisted of periodical stabbing pains in the lumbar region, radiating toward the spleen and testicle, and of areas of hyperesthesia and exquisite tenderness over the sternum, together with frequency of urination, attended by a sensation of scalding. He stated that he had lost 40 pounds in weight in the previous three months.

On admission a few enlarged lymph nodes were present on the left side of the neck and in the corresponding axilla, and smaller ones in the neck on the right side. The spleen was palpable 2½ cm. below the costal margin and as far forward as the nipple line. The inguinal nodes on both sides were greatly enlarged. In the abdomen a firm, fixed mass was felt in the left lower quadrant that was about 12 cm. in length, extending from the median line into the left flank. The same mass was palpable through the rectum. A month after admission the lymph nodes on the left side of the neck had diminished appreciably in size, while the spleen had increased so that it was palpable almost as far forward as the middle line. Cystoscopical examination showed a smooth mass which elevated the posterior bladder wall between the orifices of the ureters as far downward as the internal sphincter. Red cells numbered 2,910,000; white cells, 5200, of which 64 per cent were polymorphonuclear neutrophiles, 21 per cent small lymphocytes, 6 per cent large mononuclear cells and 9 per cent transitionals. Wassermann reaction negative. An excised lymph node revealed the histology of Hodgkin's disease.

Duration of symptoms: Seven months.

Autopsy Findings. Hodgkin's disease, with enormous enlargement of the abdominal and pelvic nodes, attended by elevation of the posterior wall of the urinary bladder; massive splenomegaly; massive solitary nodule at transverse fissure of liver surrounding portal vein; multiple small nodules in kidneys.

Histology.—Microscopical examination of the enlarged lymph nodes and of the foci in the spleen, kidney and liver showed a fine connective-tissue reticulum which enclosed a few lymphocytes and prodigious numbers of large mononuclear cells, together with a faint sprinkling of multinuclear cells of the myeloid type.

Comment. In this case the nodes in the abdomen presented an extraordinary degree of enlargement, while the thoracic nodes escaped entirely and those of the neck were enlarged to a very slight extent. Perhaps the most interesting individual feature in

the case consists in the fact that at the transverse fissure of the liver was a solitary massive nodule which surrounded the portal vein and appeared to spring from its walls. Microscopical examination of this nodule indicated that the mass in question had actually arisen as a result of hyperplasia of residual lymphoid collections in the walls of the portal vein—a fact which, taken in connection with the anatomical and histological findings in the next case to be described, emphasizes the importance of the vascular structures in the liver in Hodgkin's disease from the standpoint of histogenesis.

CASE VIII. **Predominant Enlargement of the Liver in Hodgkin's Disease.**—S. P., female, aged forty years, was admitted to Bellevue Hospital, April 12, 1921, and died twelve days later. She complained of cough of two weeks' duration, but principally of enlargement of the abdomen that had been progressing for a period of three months, attended by pains in the epigastrium and chest. At the time of admission the patient was profoundly emaciated. The skin was tinged slightly yellow. The abdomen was prominent and there were signs of a fluid wave and of shifting dulness. The lower edge of the liver was palpated at the level of the umbilicus. The spleen was not felt. After paracentesis and the removal of 4400 cc of clear yellow fluid the edge of the spleen was palpated in the anterior axillary line. Red cells numbered 2,400,000; hemoglobin, 18 per cent; white cells, 14,800, of which 59 per cent were polymorphonuclear neutrophiles, 39 per cent lymphocytes and 2 per cent transitionals.

Duration of symptoms: Three months (?).

Autopsy Findings. The abdomen contained about 500 cc of clear fluid. The liver was enormously enlarged, the lower margin resting at the level of the umbilicus. Its shape was normal. The surface was smooth, except for a number of minute whitish nodules, the largest of which were about 5 mm. in diameter. On section, the substance of the liver was permeated by large, smooth, opaque bands of fibrous tissue which followed the distribution of the portal system. At the time of necropsy it was estimated that two-thirds of the parenchyma was thus replaced (Fig. 1). On cross-section the fibrous bands were rounded in shape, often approximating the size of one's little finger, and were distinctly differentiated from the remnants of liver tissue and frequently presented at the center a minute dimple, corresponding to the cut-end of a bloodvessel. In other places were similarly rounded masses which were only a few millimeters in diameter. Between these and the larger ones were fibrous areas of different gradations in size. The liver tissue in the immediate vicinity presented evidences of compression, the lobular remnants being small and irregular in shape. In places were large reddish splotches, suggesting hemorrhagic extravasations.

The mesenteric and retroperitoneal lymph nodes were moderately increased in number and varied in size from 1 to 3 cm. On section they were firm and presented a smooth, whitish, translucent surface. No other enlarged lymph nodes were encountered. The spleen was normal in size.

Histology.—Microscopical examination of the liver showed extensive replacement of the parenchyma by connective-tissue bands which consisted of a pinkish staining, homogeneous or poorly fibrillated matrix in which were fairly large numbers of small, lightly staining nuclei of different shapes, some short and plump,

FIG. 1.—Case VIII. Photograph of tissue from the liver showing extensive sclerotic changes. The larger whitish masses represent thickened portal veins which have fused. In them the lumina are sometimes still visible as minute dots appearing black in the illustration. The smaller whitish masses likewise represent thickened veins. At necropsy, it was estimated that two-thirds of the liver substance had been replaced in this fashion. A few enlarged lymph nodes were present in the abdominal cavity and histologically showed the characteristic changes of Hodgkin's disease. The extensive sclerotic changes in the walls of the portal veins are believed to represent a new phase in the pathology of Hodgkin's disease.

others drawn out at one end, others oat-shaped, few of them clean-cut spindles. The connective-tissue bands occupied the portal spaces and expanded in such fashion as to produce pressure atrophy of the liver lobules and the bile ducts, remnants of which could be seen lying in them as streaks or islands of different shapes. In practically every one of them was a small portal vessel encircled by a mantle of lymphocytic cells, among which, in many instances,

were large mononuclear cells and, occasionally, a multinuclear giant cell (Fig. 2). In other instances the lumen of the small portal vessels was occluded or obliterated, and arranged around the remains were collections of lymphocytes, a relative preponderance of large mononuclear cells and an occasional giant-cell—the whole set in the midst of a rounded mass of fibrous tissue. In still other places, particularly in the periportal spaces between the compressed liver lobules at the periphery of the large fibrous bands, the connective tissue was arranged in small streaks or patches, and was delicately fibrillar and infiltrated by lymphoid cells, representing, apparently a localized reactive process. None of them showed the

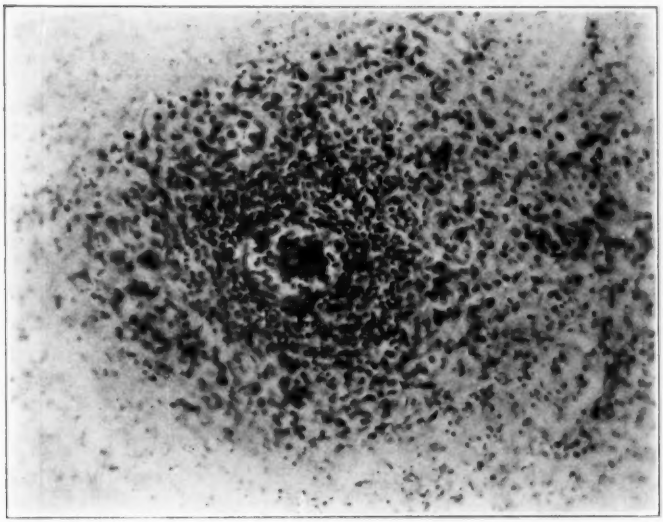

FIG. 2.—Case VIII. Photomicrograph of small portal vein surrounded by a collection of small lymphocytes, large mononuclear cells and an occasional atypical multinuclear giant cell.

histological changes of Hodgkin's disease, the latter being confined to the walls of the portal vessels or their remains. Finally, numerous hemorrhagic extravasations were visible, practically always among the compressed lobular remnants, due, apparently, to vascular injury induced by the pressure of the connective-tissue masses growing around the portal vessels. In the substance of the spleen microscopical examination showed great thickening of the larger veins, the walls of which were reinforced by poorly nucleated connective tissue in which were groups of lymphoid cells and a few cells of the large mononuclear type, together with conspicuous numbers of atypical multinuclear giant cells (Fig. 3). Microscopically the splenic pulp was unchanged. The lymph nodes

were extensively but irregularly replaced by fibrous tissue, which was poorly nucleated and presented a glazed, hyaline appearance. In the intervals were collections of lymphoid cells with an occasional mononuclear giant cell and a fairly liberal sprinkling of multinuclear cells of the myeloid type. The veins in the medulla of the the suprarenal capsule were thickened, and in their walls were collections of small round cells and, rarely, a multinuclear giant cell. In the interstitial tissues of the adrenal were irregularly outlined collections of small round cells of the lymphocytic type, but among them giant cells were not to be seen.

Comment. Comment on this case, which represents a new phase in the pathology of Hodgkin's disease, is reserved for that section which deals with the changes in the liver as a whole.

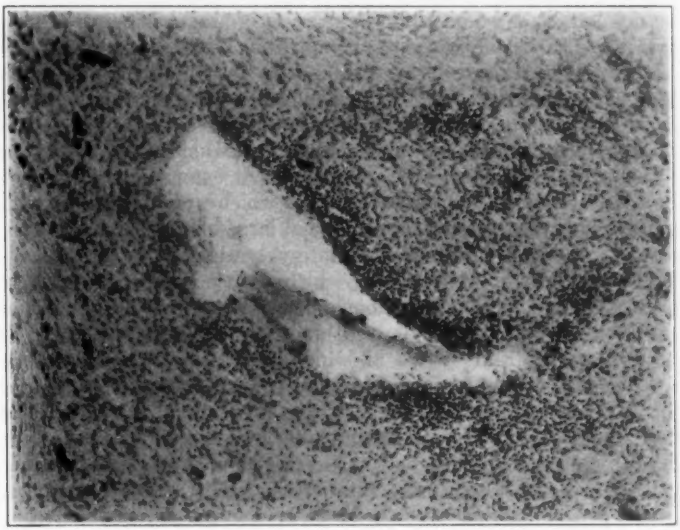

FIG. 3.—Case VIII. Photomicrograph of a thickened vein in the substance of the spleen. In the walls of the vein are collections of lymphocytes and numbers of atypical giant cells.

CASE IX. **Predominant Enlargement of the Spleen in Hodgkin's Disease.**—The patient, R. H., female, aged sixty years, was admitted to Bellevue Hospital, May 21, 1913, and died June 5, 1913. There is nothing in the clinical history of importance in the present connection, with the possible exception that the patient stated that two years previous to admission she had suffered from an attack of "malaria." At the time of admission she complained of shortness of breath on exertion, weakness and loss of weight. The temperature showed no noteworthy deviations from the normal.

Autopsy Findings. The body was that of a poorly nourished, elderly female. The skin presented a slightly bronzed appearance. There were palpably enlarged lymph nodes in the axillary, supraclavicular and inguinal regions, all of them firm, discrete and freely movable. The lower border of the liver lay on a level with the crest of the ilium. Both pleural cavities were distended by clear straw-colored fluid. In the lower lobe of the left lung, near the anterior and inferior margin, was a solitary nodule, 3 cm. in diameter, grayish-white in color. The peribronchial lymph nodes were noticeably enlarged, firm and, on section, presented a fleshy appearance. The visceral pericardium and the epicardial fat contained numbers of small, firm, grayish-white, nodular foci. The spleen was firm and greatly enlarged, weighing 657 gm. and measuring 19 by 12½ by 5 cm. On section the cut-surface presented numerous small yellowish foci. The liver was increased in size, measuring 27 by 25 by 7 cm. and weighing 2470 gm.

Histology. Microscopical examination of lymph nodes from various parts of the body showed diffuse hyperplasia of lymphoid cells, large numbers of multinuclear giant cells and of large mononuclear forms and a few eosinophiles, the whole supported by a fibroblastic reticulum. The spleen showed extensive replacement by connective tissue, scattered through which were relatively small numbers of lymphocytes, an occasional large mononuclear cell and, rarely, a myeloid giant cell. At intervals were richly cellular collections of lymphocytes, among which were conspicuous numbers of myeloid giant cells, large mononuclear forms and an occasional eosinophile. The nodule in the lung showed a fibroblastic connective tissue frame work in which were islands composed of lymphocytes with a few myeloid giant cells and large mononuclear forms. Eosinophiles were evident in small numbers. The nodules in the epicardium showed innumerable lymphocytes, considerable numbers of eosinophiles and moderate numbers of mononuclear giant cells and an occasional multinuclear cell of the myeloid type. In the perilobular spaces of the liver were large and small, irregularly outlined collections of lymphocytes, among which myeloid giant cells and large mononuclear forms were occasionally to be seen. In many places the cellular foci lay in a sclerotic reticulum; in other places the periportal connective tissues were converted into rounded or streak-like masses of hyaline material in which few, if any, cells were discernible.

Comment. Whether there is a form of Hodgkin's disease that is "primary" in the spleen has been questioned—I refer to enlargement of the spleen without involvement of the lymph nodes, or in connection with which it can be shown with reasonable certainty that involvement of the lymph nodes, when present, is secondary to enlargement of the spleen.

In 1909 I described the case of a girl, aged eighteen years, who, for a period of three years before admission to the hospital, knew that there was a mass in the left side of her abdomen.[4] Four months before entering the hospital she experienced irregularly recurring chills alternating with fever, sometimes two or three times in the course of the day. The edge of the spleen was felt 2½ cm. above Poupart's ligament on the left side, whence it could be traced 6 cm. to the right of the umbilicus and thence upward to the ensiform cartilage. No superficial lymph-node enlargements were present. The spleen, which was removed by operation, measured 25 by 18 by 8 cm. and, upon microscopical examination, presented the histology of Hodgkin's disease. At the time of operation no enlarged lymph nodes were seen or felt in the abdomen. Death occurred, but necropsy was not obtainable.

Four years later Wade[5] described the case of a man, aged fifty-five years, a resident of Louisiana, who complained of intermittent chills, fever and sweats, and enlargement of the spleen, surgical removal and microscopical examination of which showed the histological picture of Hodgkin's disease. In his case there were no superficial lymph-node enlargements, nor were enlarged abdominal nodes noted at the time of operation. No autopsy was obtained.

Three years after this Mellon[6] described the case of a girl, aged seventeen years, who, for eight months, had complained of severe pain in the left hypochondriac region and of intermittent chills and fever. The spleen was removed surgically, and microscopical examination showed the histology of Hodgkin's disease. The spleen is described as "enlarged," but its measurements and weight are not given. Mellon's description is equally vague as to the size and number of the lymph-node enlargements as revealed by necropsy, although he states that the cervical nodes were not enlarged and indicates that the inguinal nodes were only slightly enlarged. Microscopical examination of nodes removed from the chest, abdomen and inguinal region showed the histology of Hodgkin's disease. His report is too indefinite to be accepted unequivocally as an example of predominant Hodgkin's disease of the spleen with secondary lymph-node enlargement.

Cases of the type described by myself and later by Wade and Mellon, and again by myself in this paper, indicate the probable existence of a variety of Hodgkin's disease in which the lymphoid follicles in the spleen are involved to such an extent as to bring about massive enlargement of the organ, while the lymph-node enlargements are relatively insignificant. There can be no question that in certain cases there is a phase *in the clinical evolution* of Hodgkin's disease that is marked by enlargement of the spleen before the appearance of recognizable signs of involvement of the lymph nodes of the neck, chest or abdomen. In addition to the

evidence just submitted it may be mentioned that at the time of the present writing (January, 1923) there is a patient in Bellevue Hospital whose spleen reaches into the pelvis and as far forward as the mammillary line. She was under observation for several weeks with the enlarged spleen as the only clinically detectable sign of disease. Finally, a small solitary lymph node appeared in one of the anterior cervical triangles. It was removed, and microscopical examination showed the histological changes of Hodgkin's disease.

It is to be noted that several of the patients above referred to gave a history of intermittent chills and fever. This is of significance in connection with the well-recognized form of disease originally described by Murchison,[7] and since him by investigators in different parts of the world, among others by Pel[8] and by Ebstein,[9] under whose names it is all too often compounded in the annals of patronymic medicine. The syndrome of Murchison is characterized by enlargement of the spleen with or, as has been claimed, without enlargement of the lymph nodes, the histological changes in the spleen and in the lymph nodes disclosing the characteristic features of Hodgkin's disease. The condition is apt to be protracted over a term of one or two years and, among other things, is attended by periods of intermittent pyrexia lasting for two weeks or longer, in the intervals between which the patient feels perfectly well and is kept in bed only with difficulty.

CASE X. **The Association of Hodgkin's Disease with Pigmentation of the Skin Resembling Acanthosis Nigricans.** — J. N., aged thirty-five years, was admitted to Bellevue Hospital, November 1, 1922, and died December 13, 1922. The patient stated that about three months previous to admission he had "caught cold," after which he began to lose weight. On September 15, 1922, he noticed that his mouth was sore and that there was an eruption throughout the buccal mucous membrane and on the lips, and that the tongue was covered with whitish material. The patient likened the appearance of the mucous membrane of his mouth to "white boiled skin." This condition lasted three days and was followed by desquamation, leaving the mouth in an apparently normal condition. At the same time the patient noticed a "rash" on the face that spread to the neck and, at the end of about four days, had involved the entire body. According to his description, the rash was accompanied by papules which oozed watery serum, dried and fell off, leaving pigmented macules. The rash was attended by a sensation of tingling, but there was no itching. The rash disappeared from the face, but persisted over the rest of the body. At the time of the appearance of the rash in the skin and the sore mouth the patient noticed for the first time that there was swelling of the nodes on both sides of the neck, and that he felt feverish

and weak. The patient's account of the changes in his mouth and skin was substantially confirmed by his physician, Dr. Masoni, who also stated that the patient's temperature at the time varied between 102 and 104° F. A year before coming to Bellevue, however, the patient was admitted to Mount Sinai Hospital, where it is recorded, according to information courteously sent to us by the Superintendent of the hospital, that the cervical lymph nodes on the left side were enlarged. Two weeks before admission to Bellevue Hospital the patient began to have dull pains in the lumbar region and across the chest, the latter accentuated by deep inspiration. At the time of admission he also complained of pain in the abdomen, nausea, shortness of breath, loss of 40 pounds in weight, weakness and a rash on the body.

Physical Examination. No pigmentary or other changes in the mouth. Numbers of enlarged, discrete, movable nodes were felt on both sides of the neck, just above the clavicles. In both axillæ the lymph nodes were markedly enlarged and discrete. The skin was roughened and presented diffuse brownish pigmentation, involving practically the whole of the body. The face was not affected. Scattered through the skin were numbers of rounded, brownish, circumscribed macules which varied in size from 2 to 5 mm. The chest showed diminished expansion on the right side and dulness over the entire right upper lobe, attended by diminished tactile fremitus, broncho-vesicular breathing, with prolonged, harsh, hissing expiration and many moist rales at the end of inspiration. The voice sounds over this area were increased almost to bronchophony. There was dulness over the manubrium. The heart sounds were muffled. The liver was palpable 9 cm. below the ensiform and was tender. The spleen was greatly enlarged, tender and firm, reaching to the level of the umbilicus; it was palpable over an area 8 by 12 cm. A lymph node removed from the neck and submitted to histological examination showed the characteristic lesions of Hodgkin's disease. The nodes of the abdomen, chest and neck were subjected to roentgen-ray therapy on seven occasions. Blood count showed 3,800,000 red cells, 70 per cent hemoglobin; 16,200 leukocytes, of which 92 per cent were polymorphonuclear neutrophiles, 7 per cent lymphocytes and 1 per cent eosinophiles. Wassermann reaction was negative. Blood-pressure was 98/78.

Autopsy Findings. Hodgkin's disease, with massive enlargement of the thoracic and abdominal lymph nodes; moderate hyperplasia of the axillary and cervical groups; massive splenomegaly with multiple granulomatous foci; innumerable minute whitish foci in liver; small whitish focus in left kidney; multiple nodules in epicardial fat; massive thickening of pleura of upper lobe of right lung (Hodgkin's disease of the pleura); chronic interstitial pneumonitis of upper lobes of both lungs; multiple patches of miliary

tubercles in both lungs; fibrosis of peribronchial nodes on right side; bilateral hydrothorax; extensive brownish pigmentation of skin with numerous brownish black macules (acanthosis nigricans?).

Histology. The most striking feature in the histology of lymph nodes removed from various parts of the body was the extent to which they had been replaced by connective tissue. In some of them sclerosis had occurred in such manner as almost completely to convert the node into a solid fibrous mass, scattered through which were a few lymphocytes and considerable numbers of mononuclear and multinuclear giant cells. In other places the lymph nodes were more cellular and presented moderate numbers of lymphocytes, large numbers of mononuclear giant cells, many of them with pale, poorly chromatic nuclei, others richly chromatic; and a liberal supply of multinuclear myeloid giant cells and small numbers of eosinophiles and eosinophilic myelocytes. In the peribronchial nodes sclerotic areas supporting lymphocytes and mononuclear and multinuclear giant cells were found side by side with epithelioid tubercles, some of the latter presenting central areas of caseation. The pleura covering the upper lobe of the right lung was converted into dense, hyaline connective tissue with scattered islands of lymphocytes, eosinophiles and eosinophilic myelocytes, mononuclear and multinuclear giant cells. The underlying lung tissue presented numbers of sclerotic bands, in the intervals between which were alveolar remnants, an occasional embryonal alveolus and scattered collections of lymphocytes and mononuclear and multinuclear giant cells. Examination of tissue removed from other parts of the lung showed numerous interstitial epithelioid tubercles. The spleen contained innumerable whorl-like collections of fibroblastic connective tissue, imbedded in which were large numbers of mononuclear and multinuclear giant cells and a few eosinophiles and eosinophilic myelocytes. The nodules in the epicardial fat revealed histological changes identical with those in the lymph nodes. Sections of the skin showed innumerable minute brownish or brownish-black pigment granules in the lowermost layers. The epithelial covering was atrophic. The suprarenal capsules were intact. The liver contained numbers of interstitial epithelioid tubercles.

Comment. In this patient the occurrence of asthenia, low blood-pressure, nausea and muffled heart sounds, together with diffuse bronzing of the skin and localized spots of darker color suggested Addison's disease, due to destruction of the adrenals and the celiac ganglia by pressure from enlarged lymph nodes in the abdomen. At necropsy the adrenals were found to be intact and there was no pigmentation of mucous membranes observed during life or at necropsy. The celiac ganglia could not be identified and were probably submerged in the masses of enlarged nodes that lay in the immediate vicinity of the adrenals. On the other hand, the

changes in the skin bore a certain resemblance to those encountered in the so-called acanthosis nigricans—a condition described independently by Pollitzer[10] and Janovsky in 1891, and since then recognized as a clinical entity by observers in various parts of the world. It is characterized by widespread pigmentation of the skin and by pigmented verrucosities or macules and, in certain cases, by papillary hypertrophy of the mucous membrane of the mouth, without pigmentation. The cutaneous changes are usually symmetrical and affect principally the axillæ, neck, the external genitals, the groin, the inner aspect of the thighs, the back of the hands, the flexor surfaces of the elbows and knees and, occasionally, the eyelids. Two types are recognized—an adult and a juvenile—and between them are certain noteworthy differences. The juvenile form pursues a benign course and may be prolonged over years without detriment to the general health of the patient. The adult form, on the other hand, is usually fatal within a year or two and is attended by marked disturbances of health, and appears to represent the cutaneous expression of disease in the deeper parts. In 35 cases of the adult variety of acanthosis nigricans collected by Pollitzer and published in 1909[10] 21, or 60 per cent, were investigated at necropsy, and in all of them malignant growths were found in the abdomen or pelvis. In 14 cases the alimentary tract was the seat of carcinoma, in 5 cases the uterus was involved and in 2 cases the structures in the abdomen were metastasized from primary carcinomata in the breast. In an additional 6 cases there was strongly presumptive clinical evidence of malignant growths in the abdomen, but confirmation by necropsy was not obtained. Pollitzer subscribes to the theory originally advanced by Darier, that the adult form of acanthosis nigricans is due to interference with the functions of the abdominal sympathetic system, brought about by pressure from malignant growths. In the case here recorded this interpretation appears to be applicable to the changes in the skin, since the regions normally occupied by the sympathetic system, including the celiac ganglia and the paraganglia, were invaded by nodular masses which, although they represented the hyperplastic lymph nodes of Hodgkin's disease, appeared no less effectually to bring about disturbances in the sympathetic system, manifested by pigmentary disturbances in the skin of the same type as those encountered in Addison's disease and in acanthosis nigricans, and yet conforming strictly to neither, either clinically or anatomically. This case is furthermore interesting as illustrating the association of Hodgkin's disease and epithelioid tubercles, sometimes in the same microscopical field.

(To be continued.)

TUBERCULOSIS AS AN ETIOLOGICAL FACTOR IN HODGKIN'S DISEASE: A HISTORICAL REVIEW.[1]

By Willis S. Lemon, M.B. (Tor.),
SECTION ON MEDICINE, MAYO CLINIC, ROCHESTER, MINN.

After Hodgkin's first description of the disease that later was to bear his name, no interest was excited until Wilks, in England, and Bonfils, in France, reported similar cases twenty years later. Neither of these men knew of the other's work and each seemed in ignorance of Hodgkin's original article; Wilks, in fact, used museum specimens that had been described by Hodgkin from the cases of Morgan (J. S., aged nine years), Bright (E. K., aged ten years) and Addison (T. W., aged fifty years). The following ten years were more productive, and case reports were written by Wunderlich, Pavy and Potain, and in 1865 a second report by Wilks appeared, in which the disease was recognized as an entity and the name "Hodgkin's disease" suggested.

In spite of the confusion always existing under such circumstances, the clinical details had been very well worked out, and Wilks, Trousseau and Wunderlich had differentiated the disease from leukemia, syphilis, malignant forms of lymphosarcoma and tuberculosis. This Hodgkin had failed to do, and in his description had included such diseases, especially tuberculosis and syphilis. The disease was regarded as a variety of lymph-gland tumor, associated with splenomegaly and an enlarged liver, and accompanied by anemia, fever and progressive loss in vitality.

Hodgkin's own description of the clinical findings and his speculation as to the cause of the disease cannot better be described than by quoting from his paper: "As far as could be ascertained from observation, or from what could be collected from the history of the cases, the enlargement of the glands appeared to be a primitive affection of these bodies rather than the result of an irritation propagated to them from some ulcerated surface or other inflamed textures through the medium of their inferent vessels, and that although in some instances the glands so enlarged may contain a little concrete inorganizable matter, such as is known to result from what is called scrofulous inflammation, it is obvious that this circumstance is not an essential character, but rather an accidental and concomitant to the idiopathic interstitial enlargement of the absorbent glandular structure throughout the body. That unless the word inflammation be allowed to have a more indefinite and loose meaning than is generally assigned to it, this affection of the glands can scarcely be attributed to that cause, since they are

[1] Read before the Muncie Academy of Medicine, Muncie, Indiana, May, 1923.

unattended with pain, heat and other ordinary symptoms of inflammation, and are not necessarily accompanied by any alteration in the cellular or other surrounding structure, and do not show any disposition to go on to the production of pus or any other acknowledged product of inflammation except where, as in the cases above alluded to, inflammation may have supervened as an accidental affection of the hypertrophied structure. . . Notwithstanding the different characters which this enlargement may present, it appears nearly in all cases to consist of a pretty uniform texture throughout, and this rather to be the consequence of a general increase of every part of the gland than of a new structure developed within it, and pushing the original structure aside, as when ordinary tuberculous matter is deposited in these bodies. At the same time it must be admitted that the new material by which the enlargement is affected presents various degrees of organizability, which in some instances is extremely slight, and appears incompetent to maintain the vitality of the affected gland."

Malpighi was of the opinion that the involvement of the spleen, with its characteristic island of lymphoid material resembling miliary tubercles, was associated with the glandular affection but might appear later in the course of the disease. He explained the absence of splenic disease by assuming that death might occur from the ravages of the disease before the onset of pathological changes within that organ.

Wilks, in his first paper, in considering lardaceous disease and its allied affections, makes a division into different classes. In his Class V are cases of a peculiar enlargement of the lymphatic glands often associated with diseases of the spleen. He subdivides Class V into two groups: (1) cases associated with lardaceous disease and tuberculous affections; and (2) those with a peculiar disease of the spleen, appearing to constitute a special form of malady.

We give credit to Markham, who reported a similar condition, and in the speculation regarding its cause, remarks: "There was little evidence to show that they were malignant and not stronger than they were scrofulous."

Wilks also quotes *verbatim* Bright's description of the various forms of the disease displayed by the spleen and of one variety which seems to be identical with that referred to by Hodgkin. Bright, however classifies the disease as malignant, and says: "There is another form of disease which appears to be of a malignant character, though it varies from the more usual form of malignant disease, and which has been particularly pointed out by Dr. Hodgkin as connected with extreme disease of the absorbent glands, more particularly those which accompany the bloodvessels. The whole of these absorbent glands become larger and firmer, without any tendency to suppurate, as in ordinary scrofulous disease, or to soften, as in cerebriform disease; at the same time, the spleen

becomes more or less completely infiltrated through its whole substance with a white matter, with almost the appearance of suet. This matter insinuates itself into the cellular structure of the spleen, but it is no easy matter to point out what particular portion of the structure receives it. A section of the organ seems to show, from the irregular forms assumed, that it fills a cellular structure, and in some degree takes its shape from the cells into which it enters, having less tendency to assume the form of regular globular masses or tubera than other malignant disease."

Wilks, on the other hand, describes in minute detail not only the progress of the disease, but also its differentiation from scrofula: "The enlargement of the glands is in most cases gradual, extending sometimes over a period of two, three or more years, and often, from commencing in the neck in tuberculous, weakly children, is called scrofulous. When the mischief is thus gradual in its commencement, and affecting only part of the glandular system, no marked symptoms ensue, but as time tends to its development in the thoracic and abdominal glands a slow prostration ensues, terminating in death. The glands often reach an enormous size, much larger than when affected with scrofula, a bunch of them often being composed of separate tumors, each the size of an egg. When felt during life, in their early progress, they are recognized by their peculiar elastic feel, differing both from the early hardness or the subsequent softness of scrofulous glands."

Following a very excellent description of the progressive development of the disease, both from its anatomical characteristics and constitutional effects, he concludes: "We have been content, therefore, with briefly stating the main facts connected with a particular class of disease, including several morbid conditions whose identity is not proved, but whose close relationship appeared to warrant the adoption of the present method of narration, in order to fix attention to them. First, there are the cases of simple lardaceous disease occurring alone; then those associated with tuberculosis; then those cases connected with disease of bone; afterward those found in connection with a peculiar affection of the glands; and, lastly, those cases where this latter condition of the glands occurred unassociated with lardaceous disease (unless white deposit in the spleen be a modification of it), but allied to the previous classes by a close relationship."

In Wilks' second paper, he says: "It is true that enlarged glands may be met with in various forms of disease, and sometimes with the lardaceous, and thus the two affections may have relationship; these would appear, also, to have a likeness to tubercle on the one hand, and cancer on the other. It is, however, as much a disease *sui generis* as any other and deserves a description of its own. . . As regards its degree of malignancy, it appears to take a place between cancer and tubercle, the growth in the glands,

with implications of the bronchial tube and pulmonary tissue, resembling the former, while the mode of deposit in the splenic corpuscles and along the minute vessels of the portal system of the liver resembles tubercle.

"In this way this disease of Hodgkin is clearly separable from lardaceous disease, from cancer and tubercle, although all these affections may bear a relation to one another. Its association with tubercle is seen in the class of organs and the tissues affected, and even by the presence of deposit in the lungs, which may be in fact real tubercle."

Pavy noted, as suggestive of Hodgkin's disease, certain features which are accepted today, particularly the extreme pallor or anemia and the enlargement of one or more lymphatic glands, either internal or external, with enlargement of the spleen, and says: "The enlargement of the lymphatic glands, which thus seems the peculiar feature of this malady, is remarkable for the lingering form of fatal cachexia which it produces.

"It may gradually extend over a period of two or more years when the thoracic and abdominal glands become involved, and slow prostration precedes death."

In the early days the disease was known under many names, depending on the author's fancy, and these names are still in use and still cause confusion. On this phase Longcope and McAlpin say: "From the time of the first comprehensive description of this disease by Hodgkin, in 1832, the affection has been designated by a great variety of names, which, during the early history of the disease, led to considerable confusion. Most of these older terms, such as 'malignant lymphoma,' 'pseudoleukemia' and 'lymphadenoma,' have been relinquished, and the disease is now widely known as Hodgkin's disease. In Germany the name 'lymphomatosis granulomatosa' or 'lymphogranulomatosis' is employed. In England the term 'lymphadenoma' is still retained."

However, certain similarities began to be pointed out which showed the close relationship to tuberculosis. Hilton Fagge, in 1874, described a primary glandular tuberculosis that, clinically, could not be differentiated from Hodgkin's disease. In his case the glands were large, remained discrete, had no periglandular infiltration and appeared in the areas usually the site of Hodgkin's disease.

Ten years later Weigert described a case that apparently belonged to the pseudoleukemias, but on section showed evidence of tuberculosis or a bacillus resembling that of tuberculosis. Three years later Delafield made a similar observation, describing a primary glandular tuberculosis, and within the next few years many others noted the striking similarity in the two types of adenopathy.

Delafield's case was interesting because of the difficulty in diagnosis and the unusual character of the tuberculosis affecting the patient. He used Dr. Ball's description because it was indicative

of the difficulty of diagnosis. In the same description, Dr. Ball mentions the fact that typhoid fever could be early excluded and that general tuberculosis was considered, although no evidence was found except in the enlargement of the cervical lymph glands and in the spleen. These glands were hard, tender, freely movable, gradually increasing in number and associated with anemia. Later in the disease the axillaries and inguinals became involved. The possibilities finally were reduced to two: either tuberculosis confined to the glandular system or Hodgkin's disease in an acute form, the latter being more plausible because of the rarity of so restricted a form of tuberculosis. In his note, however, he reports cases of acute Hodgkin's disease described by Gowers and Hilton Fagge. He says in conclusion: "Some cases of this kind are described by the older authors under the name of acute scrofula. Others have been confounded with the morbid condition known under the names of Hodgkin's disease, pseudoleukemia, adenia, anemia lymphatica, lymphadenoma and malignant lymphoma. A few cases similar to the one here reported have been described by Hilton Fagge and Pye Smith."

Sternberg, in a long article, reviews the literature, and describes the studies on etiology, including many forms of organisms, that had been undertaken up to his day. He rejects these explanations of the etiology of the disease and concludes that Hodgkin's disease is a peculiar type of tuberculosis. Of his 13 cases of pseudoleukemia, 8 revealed the presence of tuberculosis in one or more organs, or the bacillus itself was found within the glands. This opinion was destined to have a very powerful influence on the later conception of the disease, an influence felt even to the present day. However, a number of his contemporaries, Weishaupt, Westphal, Dietrich and Fischer, modified his view somewhat; Westphal because the *Bacillus tuberculosis* was absent in most examinations and because inoculation experiments were failures in most cases. These authors were of the opinion that tuberculosis might be a factor, but that it appeared as a secondary invader.

Andrewes also refused to accept the Sternberg hypothesis, and offered as explanation for the presence of the *Bacillus tuberculosis* the belief that the lymphatic gland acts as a filter for bacteria. Therefore, the finding of tuberculosis bacilli in the gland proves only the germ's presence, not that the gland itself is tuberculous.

That the patient may have tubercular glands, but not be tuberculous, was shown by Pizzini, who used glands from necropsies of people who died from other diseases, and found 42 per cent positive for tuberculosis. Of the glands studied, the tracheo-bronchial glands gave the highest percentage of positives. Such a finding is in agreement with the experience of pathologists at the present time, and with the anatomical studies on tuberculosis of Ghon, in Germany, and of Opie, in this country.

In 1891 Northrup reached similar conclusions, finding tuberculosis limited to the bronchial lymph glands in 13 of 125 necropsies on tuberculous children who died of non-tuberculous diseases, and Holt, in 1903, reports having seen similar findings. Loomis, in a necropsy study of 30 persons who died from violence or acute disease, found 8 whose bronchial glands produced tuberculosis in inoculated animals, although in the patients there was no evidence of tuberculosis outside the glands.

Sailer, however, in 1902, thought the majority of cases were due to tuberculosis. He says: "That certain of the cases are due to a peculiar form of tuberculosis of the lymphatic apparatus has been recognized for a considerable length of time, chiefly as a result of the brilliant article of Sternberg; but such cases have been considered rather as pathological curiosities than as clinically recognizable. The majority of cases have been diagnosed pseudoleukemia, and only the necropsy has revealed the true condition. . . .

"That the glands in many instances contain tubercle bacilli is no longer a matter of question, and that these bacilli are capable of infecting susceptible animals has been conclusively proven. Moreover, it has been shown that in many cases with the characteristic histological picture of lymphoma, tuberculosis exists, and the tubercle bacilli may be numerous and virulent. It does not necessarily follow that they are the cause of pseudoleukemia, because, as many authors have suggested, they may exist either as a secondary or as an associated infection. That is to say, there is no reason why lymph glands, the seat of tuberculosis, might not take on the changes and produce the symptoms of a pseudoleukemia, or that lymph glands characterized by the morbid laterations of pseudoleukemia and associated with symptoms of that disease might not become infected with tubercle bacilli." We are in complete agreement with this last statement.

Another explanation for the presence of tuberculosis in the glands of patients with Hodgkin's disease was offered by Parkes Weber. He believed that lymphadenomatous tissue offered a soil favorable to the growth of tuberculosis bacilli, and that they were able to establish themselves and flourish in glands affected with Hodgkin's disease. Thus, children with Hodgkin's disease ultimately develop fatal disseminated miliary tuberculosis. In explaining his belief, he quotes Quincke's view that the development of tuberculosis in Hodgkin's disease sometimes causes retrogression of the lymphadenomatous process, as was observed in patients with leukemia who became tuberculous. The finding of tuberculosis bacilli therefore does not prove that the original disease may not have been lymphadenoma.

Further evidence of the distinctiveness of the two diseases appeared with the reports of Reed, Longcope and Simmons. In Reed's series of 8 cases of Hodgkin's disease, 1 patient died of

miliary tuberculosis. There was no tuberculosis in the other 7 cases, 5 of which came to operation, and 2 to necropsy. Two inoculation experiments also failed to produce tuberculosis. In Longcope's series of 8 cases tuberculosis was not found in any, although 4 came to necropsy, and 4 inoculation experiments were made.

In Simmons' 9 cases there were 5 negative inoculation experiments, and in Warnecki's 9 cases 4 negative inoculations; 1 patient, however, had apical tuberculosis.

On the other hand, Yamasaki found small foci of tuberculosis in bronchial glands, lung apices, or intestines in 4 of 6 necropsies. Such a report, however, must be considered in the light of the work of Ghon, Opie, Pizzini, Northrup and Loomis.

In 1914 Wuttke concluded that Hodgkin's disease is an infection due to a modified strain of tuberculosis bacilli, whose exact relation to the usual form has not yet been established. To support this contention, he quoted Mallory's definition given in a personal communication: "It is a name applied to a clinical condition. Some of the cases turn out to be tuberculosis; a few are cancer or other malignant tumors. The majority turn out to be lymphoblastoma." Wuttke also obtains support from O. Meyer and K. Meyer, who obtained the Much granule, repeatedly reproduced it in guinea pigs, and in their third case found tuberculosis; also from Heinz, who, using the antiformin method, found human tuberculosis; and from Löffelmann, who in 7 cases of Hodgkin's disease observed positive tuberculosis in 6 and the Much granule in 1. Errors may have crept in because of technical difficulties. It is possible that the peculiar cultural and staining reactions of such organisms may be explained as suggested by Gaarde, who said: "The diphtheroid bacillus obtained in the culture of Hodgkin's glands, when grown in egg-yolk media which contains fat, sometimes has a tendency to become acid-fast when stained with carbol fuchsin. Unlike tubercle bacilli, they are rather easily destained, yet are much more resistant to destaining with acid alcohol than the common bacteria."

As late as 1921 Loygue states that the etiology is uncertain, but in the absence of any proof of any specific cause for Hodgkin's disease, a tuberculous origin would seem to be the most likely.

Symmers considers that both the tuberculous and the diphtheroid organism theory have failed of confirmation, and defines his conception of the nature of the disease as follows: "Hodgkin's disease is neither infectious nor neoplastic, but a systemic disease expressing a predilection for lymphoid tissue, giving rise to multiple foci of growth at approximately the same time in response to the same provocative agent."

Clinical Similarity of the Adenopathy in Tuberculosis and in Hodgkin's Disease. When a patient with adenopathy appears for diagnosis the examiner must consider the possibility of Hodgkin's disease, lymphosarcoma, lymphatic leukemia, syphilitic adenopathy,

true malignancies (either carcinoma or sarcoma) and tuberculosis, in making a differential diagnosis. Many times the clinical examination is insufficient, and a biopsy must be made before a diagnosis can be obtained. One of the most clinically characteristic cases of Hodgkin's disease that has come to my attention proved on blood examination and biopsy to be lymphatic leukemia. Yet the distribution of the adenopathy, the progress of the disease and the presence of pruritus were characteristically those of Hodgkin's disease. Of 191 patients, either seen personally or whose records have been available to me for study, tuberculosis of the glands had to be taken into account in a considerable number. This was especially true in a case of Hodgkin's disease which gave evidence of marked tenderness on palpation of the glands. I believe that difficulty in differentiating tuberculosis and Hodgkin's disease is a common experience of examiners. Longcope says: "Of all types of glandular enlargement, the one most often mistaken for Hodgkin's disease is tuberculosis. Sometimes indeed, from a clinical examination alone, it is impossible to tell the affections apart."

In my series a differential diagnosis from lymphosarcoma has proved the most difficult. Often the pathologist's report must be obtained before a decision can be reached. It has been my experience that such a report on one examination of tissue may be reversed at a later time when another gland is examined, and MacCarty is of the opinion that the lymphosarcoma and Hodgkin's disease may be but different manifestations of the same condition. Certainly this seems true from a consideration of the progress of the disease.

The similarity to tuberculosis applies to three types of that disease: (1) An acute, comparatively rare form in which the glands swell rapidly, appear on both sides of the neck (beginning in the nodes beneath the jaw and in the anterior triangle) are painful, tender to touch and associated with fever. These glands are regular, oval, firm but elastic, remain discrete, and on section reveal shiny raised points which are in fact typical miliary tubercles (Longcope). (2) The disease as described by Delafield and Fagge may exactly simulate Hodgkin's. In this type the tumors may be large and hard, appear in all gland-bearing areas, often remain discrete and without evidence of periadenitis, and yet on removal are found to be entirely caseous. (3) Patten and Bissel have reported a peculiar adenopathy occurring in negroes, which resembles in course and clinical features various types of glandular involvement, but more especially the leukemias, and which eventually proves to be tubercular. Nearly all the lymph glands are involved, but there is little or late involvement of the internal organs. The glands are elastic, smooth, ovoid or globular, unattached, painless, and are not tender, nor does suppuration occur. They are lobulated, as in Hodgkin's disease, and are associated with slow or rapid cachexia, continuous or irregular fever and increasing anemia.

There is usually no confusion regarding the typical tuberculous adenopathy with its caseation, suppuration and sinus formation, but 1 case of Hodgkin's disease was observed in my service that appeared as a large phlegmon of the neck associated with suppuration and multiple sinuses, in which the diagnosis of Hodgkin's disease was made by biopsy on the gland.

Pathology. Adami, in his discussion of tumors originating from tissue-producing lymphocytes, divided them into seven classes: (1) Chronic hyperplasia, of which some of the best examples are seen in connection with two forms of tuberculosis: (*a*) Specific granulomatous changes with caseation; (*b*) diffuse enlargement without caseation, but revealing fibrosis, increase of endothelial elements, and decrease of lymphatic elements (the paratuberculous lymphadenitis which is an overgrowth response to the stimulus of tissue). (2) Hodgkin's disease, in which an unknown irritant produces the hyperplasia; the marked feature is the reticular and connective-tissue overgrowth similar to what is noticed in the tuberculosis group. (3) A type of gland resembling Hodgkin's disease microscopically, but on intensive staining, showing the *Bacillus tuberculosis*, the granulomatous hyperplastic lymphadenitis of Ewing. (4) Leukemia, an overgrowth of otherwise normal lymphadenoid tissue, and a passage into the blood of large numbers of lymphocytes. (5) Typical lymphoma. (6) Lymphosarcoma. (7) Lymphosarcomatosis. Such a conception permits of borderline types that may be difficult of classification, either from the clinical or the pathological viewpoint.

When the pathological picture was made definite by Reed, Longcope and Simmons, their description of the first stage was remarkably similar to that of an inflammatory state. They described the hyperplasia of the lymphoid cells with active proliferation in the germinal centers, the increase in vascularity, the proliferation of reticular endothelium, the dilatation of the lymph sinuses which are crowded with lymphocytes, both small and large, polymorphonuclear leukocytes, eosinophiles and endothelial cells, a description not unlike that of early inflammation. A node due to an early first stage of Hodgkin's disease is very difficult to differentiate from the hyperplastic lymph node of toxemia, or the inflammatory reaction, or from lymphatic leukemia. In the late stage of Hodgkin's disease, confusion is possible because of the presence of fibrosis, accumulation of lymphocytes and Reed giant cells, that may simulate the Langhans cell of tuberculosis.

Clinical Observations at the Mayo Clinic. In October, 1921, Doyle and I became interested especially in the mediastinal involvement of Hodgkin's disease, and inquired into the history of such patients in order to determine how often tuberculosis was an etiological factor, or an associated disease. Of more than 26 cases, in which mediastinal involvement was observed, only 2 knew of tuberculosis in the family; 1 of these reported that a cousin had had tuber-

culosis of the cervical glands, and another believed that a maternal aunt had died of pulmonary tuberculosis. Roentgen-ray examination revealed evidence of tuberculosis in only 1 patient, and this finding could not be confirmed by clinical or microscopical examination. Moreover, at necropsy no evidence of tuberculosis was found in 3 instances.

In only 1 other case which I have observed was tuberculosis clinically evident during the course of the disease. This case was not included among the 26 because there was no clinical evidence of mediastinal involvement.

A summary of 191 cases of Hodgkin's disease was recently made, and in only 8 was there evidence of tuberculosis. This evidence was seen in roentgenograms of the chest. However, in a review of 191 unselected routine cases comprising many different diseases, the roentgenograms of the chest revealed evidence of 17 cases of tuberculosis in either healed or open form. This would seem to indicate that tuberculous involvement of the mediastinum is not as common a complication in Hodgkin's disease, as in other diseases, but in making such a comparison one must keep in mind the infrequency of pulmonary tuberculosis in cases of glandular involvement with that disease.

Conclusion. There are many similarities between tuberculous adenopathy and that of Hodgkin's disease, which are often very confusing to the clinician, and occasionally to the pathologist, but I believe that infection with tuberculosis bacilli does not produce Hodgkin's disease, although the two diseases may be associated.

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MANAGEMENT OF THE DIABETIC PATIENT, WITH ESPECIAL REFERENCE TO THE ADMINISTRATION OF INSULIN.

By Willard C. Stoner, M.D.,
CLEVELAND, OHIO.

The advances made in the problem of diabetes in the last ten years have given us a rational and satisfactory treatment of the disease. Previous to the work of Allen, in which he emphasized the importance of undernutrition in managing these cases, there was no satisfactory standardized treatment. The management consisted largely of the use and obviously abuse of drug therapy which was instituted without rhyme or reason. And while it is true that considerable attention was given to dietary management no satisfactory dietary regimen was uniformly practised even in our large clinics, and notwithstanding criticism that undernutrition treatment of disease is not treatment, the work of Allen must stand as the important background of our dietary management.

The work done on depancreatized animals by Minkowski and von Mering was confirmed by Allen and thus the absolute pathological change as being limited the pancreas was definitely established.

The work of Banting and his co-workers have given us a specific serum, insulin, which is a most valuable adjunct in the treatment of these cases, however, the observations to date do not indicate that the administration of insulin can in any way replace dietary management. There are certain fundamental facts in the management of the disease that are not generally known. It has been my observation that it is not common knowledge that alkalis are contraindicated in the routine management unless it be in coma, and then of rather limited value; that there is not a single drug that has value in treatment except as indicated for coexisting conditions that arise, such as failing myocardium in coma where digitalis may be indicated.

Blood-sugar estimations have become a routine in most hospital clinics and the necessity for these estimations in the management of these cases should be understood. It is important to do blood-sugar estimation to determine blood-sugar level and kidney threshold. It is important to do blood-sugar estimations to differentiate renal diabetes and glycosurias from diabetes mellitus. And while the writer does routine blood-sugar estimations at intervals on all diabetics whether insulin is administered or not, I do not believe it is a necessity for the satisfactory management of these cases. Blood-sugar level is an everchanging factor and as Newburg has pointed out that unless one has repeated observations in the twenty-four hour period, determinations do not represent the true level. Observation has shown that blood-sugar level in normal individuals

is at variance, and while we consider 100 mg. to 125 mg. per 100 cc of blood taken in the morning after no food for ten or twelve hours as being the normal blood sugar, we should not split hairs on slight variations; neither should we expect to maintain the moderately severe diabetic under the most careful dietary management with a blood-sugar level around 100 mg. These patients must be managed so that their strength and nutrition will not be impaired to the extent of incapacitating them for work.

Diabetes is a disease that effects individuals in all walks of life and the prevalence of the disease among the wage-earner makes the economic aspect an important one. It is a chronic disease and we cannot hope to obtain a cure in most cases even with insulin; therefore our management must take into consideration this factor. We cannot hope to hospitalize these cases unless severe and incapable of doing work for long periods of time. Fortunately it is not necessary to hospitalize to any great extent except the severe cases and the cases with complications, as coma. There is a certain disappointment that comes to the patient who has been hospitalized in the initial management. He very often feels that he has had a cure by reason of his stay in a hospital and this has been especially true since the administration of insulin. Unfortunately the idea has been conveyed to the laymen, I think largely through the lay press that insulin represents a cure and this brings disappointment.

Most diabetics can be safely and satisfactorily managed in an ambulatory clinic; they can be safely rendered urine sugar-free; they can be instructed in satisfactory dietary management; they can be furnished insulin and have it administered in the home, once or twice daily, without any risk; they can be instructed to test their own urine daily for sugar and whenever sugar appears to have a half-day of semi-starvation. It is important to have them appreciate the need of frequent checks to know that they are satisfactorily carrying on. The management should be so simplified that the patient can carry on without consuming too much of his time trying to live within his carbohydrate tolerance. If he must weigh every morsel of food and do other needless things, sooner or later he will cease to coöperate, lose interest in his condition and undo all the good that has been done. It has been my experience that most cases of diabetes will coöperate if given the right kind of help.

I know of no disease where individualization in management is so important as in diabetes and in no chronic disease are we so well rewarded for our efforts in management. I do not think it necessary or practical in most cases to hope to maintain a blood-sugar level much below an average of 200 mg. per 100 cc of blood, providing the urine is maintained sugar-free and without acid bodies.

We have managed 43 cases of diabetes, including 3 cases of coma with recovery, in St. Luke's hospital and my private clinic, since November, 1922, to which varying quantities of insulin have been administered. We have not found it necessary or practical to hos-

pitalize all these cases on instituting management and I am convinced that one can safely manage a large per cent of diabetics as ambulatory cases from the start. If one has a satisfactory dietary regimen to place in the hands of the patient and gives the necessary instruction to have him know the simple facts about his disease, he will coöperate just as well and you will save him time as well as money.

Much caution was emphasized about the dangers of the administration of insulin earlier which fortunately has been minimized with experience and now the family doctor as well as the patient safely administers it. In this series of cases we have seen no untoward symptoms arise following the administration except transitory sweating, vertigo, slight vasomotor disturbances, hunger and weakness. These symptoms have not been constant in individual cases and were not in relation to hypoglycemia. Most marked symptoms occurred in hyperglycemia cases where the blood-sugar level was over 200 mg. per 100 cc of blood. The symptoms occur about one hour after administration and no doubt represent the effect of abruptly burning up sugar. The following dietary mangement, in a general way, has been a routine with individual modifications.

Before instituting insulin treatment the patient was maintained on a liter of whole milk daily given at two- or three-hour intervals until urine is sugar-free. Water is taken very freely. The ordinary case is urine sugar-free in twenty-four hours and the more severe in forty-eight or seventy-two hours. This has furnished a very satisfactory dietary to determine blood-sugar level. When urine is sugar-free, insulin administration is begun in ten-unit doses daily or twice daily, subcutaneously, preferably in loose tissues at angle of arm in order to avoid welt and encourage delay of absorption.

A dietary is pursued, with certain modifications, such as is being used by the Massachusetts General Hospital. The carbohydrate, protein, and fat quantity is determined on the basis of weight, severity, activity of the patient, and insulin administration. The following table brings out detailed facts.

The age of this series of 43 cases varies from ten years to seventy-three years with an average age of fifty years.

The duration of the disease as evidenced by recognition on the part of a physician or history of symptoms varies from one month to twenty-five years, with an average of five and a half years.

Weight: 17 patients remained constant in weight; 17 patients gained in weight; 9 patients lost in weight.

Onset: 12 cases were characterized by abrupt onset; 31 cases were characterized by insidious onset.

Severity: 2 cases were mild; 22 cases were moderately severe; 19 cases were severe; 3 cases of this series of 43 cases were in coma, however all recovered.

Previous management: 5 cases had not been managed previously; 4 cases were managed satisfactorily; 22 cases were managed unsat-

isfactorily; 12 cases showed a fair response to previous management.

Blood-sugar levels before management:

	Case.
150–200 mg. sugar per 100 cc blood	1
200–250 mg. sugar per 100 cc blood	7
250–300 mg. sugar per 100 cc blood	4
300–350 mg. sugar per 100 cc blood	11
350–400 mg. sugar per 100 cc blood	6
400–450 mg. sugar per 100 cc blood	8
450–500 mg. sugar per 100 cc blood	3
600–650 mg. sugar per 100 cc blood	2
750–800 mg. sugar per 100 cc blood	1

Blood-sugar levels after management:

	Case.
50–100 mg. sugar per 100 cc blood	7
100–150 mg. sugar per 100 cc blood	15
150–200 mg. sugar per 100 cc blood	12
200–250 mg. sugar per 100 cc blood	3
250–300 mg. sugar per 100 cc blood	3
300–350 mg. sugar per 100 cc blood	1
350–400 mg. sugar per 100 cc blood	1

Acid bodies in urine before management: 16 cases showed acid bodies in the urine before management; 27 cases were free of acid bodies.

Acid bodies in urine after management: 3 cases showed acid bodies in the urine after management; 40 cases were free of acid bodies.

Urine sugar before management: 41 cases showed an average sugar of 4.2 per cent; 2 cases were sugar-free.

Urine sugar after management: 14 cases were sugar-free continuously; 5 cases had an average sugar from 0.1 per cent (min.) to 3.5 per cent (max.); 24 cases had an average sugar from 0.0 per cent (min.) to 2.2 per cent (max.).

Insulin administration: The quantity of insulin administered to an individual case varied from ten to sixty units. The smallest total quanitity given an individual case was 72 units, and the largest total quantity was 1945 units. A number of cases are supplied with 2 cc syringes and insulin with instructions to administer once or twice daily at home. The dosage varies from 1 cc to 2 cc or 10 to 20 units given preferably at breakfast and dinner-time. All cases are checked on blood sugars from time to time.

Caloric intake: The daily caloric intake has varied from 756 calories to 2479.2 calories.

Response to treatment: With one exception all the cases have responded to treatment in a very satisfactory way. The one case of coma responded after being in coma for a period of four days. The response of a profound coma case to insulin administration is the most spectacular demonstration in clinical medicine. The value of

insulin in diabetic coma is superior to most specific sera that we have for any given disease.

Case VI, a moderately severe case did not respond well to the administration of insulin. At first he improved materially, then he lost in weight, his tolerance lessened, his general appearance was not so good, he complained of tire and finally dropped away from the clinic, however he had no other untoward signs.

Case IX, a severe case and who was unsatisfactorily managed in two clinics previously responded to management very satisfactorily. She gained in weight, returned to work but later developed an active pulmonary tuberculosis. It is interesting to note that her weight has been maintained by the administration of 60 units of insulin daily which has allowed a high caloric intake. However her pulmonary condition is unaffected by management.

Case XV was an alcoholic and failed to coöperate on diet, however, his general condition was much improved with insulin administration.

Case XX, a girl, aged ten years, who was a severe case and developed coma was cleared up in twenty-four hours during which time 100 units of insulin were given, afterward developed scarlatina and made a good recovery.

Case XXV, a girl, aged thirteen years, with severe diabetes, abrupt onset, improved materially so that she is urine sugar-free on a practically unrestricted diet.

Case XXVI was managed over a period of years, improved under former dietary management and was restored to work part of the time. His improvement under insulin was remarkable and he has returned to full-time work with weight-gain in spite of a relatively high blood-sugar level.

Conclusions. 1. With our conception of dietary management and the use of insulin, diabetes is no longer a bugbear in practice.

2. While insulin does not give promise of a cure, it improves the mental and physical state of all patients suffering from the disease in a manner that justifies its administration routinely.

3. With a proper conception of dietary management and the proper administration of insulin we can save most cases of diabetic coma and safeguard cases where surgical procedures are necessary.

4. Diabetes being a chronic disease not curable, hospitalization should be reduced to a minimum and emphasis placed on the patient becoming his own doctor.

PERFORATION OF THE ESOPHAGUS DUE TO INSTRUMENTATION (WITH A REPORT OF THREE CASES).[1]

By Julius Friedenwald, M.D.,
Professor of Gastro-enterology, University of Maryland,
and
Theodore H. Morrison, M.D.,
Associate in Gastro-enterology, University of Maryland,
Baltimore.

(From the Gastro-enterological Clinic of the Department of Medicine of the University of Maryland.)

Numerous cases of perforation of the esophagus, due to the application of the stomach tube, dilator, bougie and esophagoscope in investigating and treating esophageal or gastric lesions, are recorded in the literature. However, the dangers involved in this character of investigation with certain forms of apparatus, especially in some affections of the esophagus, do not appear to have been sufficiently emphasized. It is on this account that the following three cases appear of sufficient interest to warrant publication.

Case I.—*Cancer of the Esophagus with Perforation into the Left Pleural Cavity and Death from Pyopneumothorax.* Mrs. J. H., married, aged thirty-one years, presented the following history: Her family and personal history were negative. She had always enjoyed good health until three months previous to admission, when difficulty in deglutition was first noted. At first this was only observed with solid food, and finally, after two months, there was absolute inability to swallow solids, while even liquids were now passed into the stomach with difficulty. Recently the act of deglutition was accompanied with great pain; frequent regurgitation of mucus occurred, but never of blood. There were constant eructations and obstinate constipation. On examination the patient was found to be well nourished; the glands are nowhere enlarged; the mucous membranes are red; the heart, lungs and abdomen are normal. The blood examination shows 5,000,000 red corpuscles and 10,000 white cells, with the urine normal. In introducing the soft tube, a resistance was felt, through which the tube could not be passed. When measured this was found to be 36 cm. from the teeth. Attempts were made to introduce various sizes of soft-rubber tubes which, however, could not be passed through the stricture. The hard tubes were then introduced. The large-sized bougies could not be passed into the stomach,

[1] Read at the annual meeting of the American Gastro-enterological Association, April 30, 1923.

but those of small size were passed without difficulty. The obstruction was constantly located at from 36 to 38 cm. from the teeth. The second deglutition murmur was delayed often to forty seconds, and at times it was entirely absent.

The patient was frequently seen, and constantly complained of pain in swallowing and of great difficulty at times of getting even the smallest quantity of milk into the stomach. It became difficult finally even to pass the small-sized bougies.

Inasmuch as the patient was now able to swallow only extremely small amounts of liquid nourishment, gastrostomy was decided on. At the time of operation even a small-sized bougie could not be passed while the patient was under anesthesia. A gastrostomy was performed and a small olive sound passed from below upward, when an obstruction was noted about 10 cm. above the cardiac orifice of the stomach. The bougie was passed through the strictured area; a string was attached to it and withdrawn, and larger sounds were then drawn through from below, attached to the cord, until the largest passed with ease. In passing the first or second sound something was felt to give away. The stomach was sutured to the abdominal wall and closed.

The patient did well for four days. Her temperature had remained between 99° and 100°F. and her pulse 100 to 108, and she was able to retain small amounts of egg albumen, milk and broth. On the fifth day she complained of intense pain in her left chest. There was a marked dyspnea and the temperature rose to 103°F., and the pulse to 140. A pyopneumothorax was discovered in the left chest and a quart of brownish pus aspirated.

On the following morning a rib at the angle of the scapula was resected, when a large quantity of foul-smelling pus was evacuated. The patient did not rally from the operation; her temperature rose to 104° F. and her pulse to 160; she died on the following morning.

At autopsy a perforation was noted in the cancerous mass in the esophagus. This mass was ulcerated, the largest diameter being 1.5 cm. in length. The circumference of the ulcer was very hard and indurated; the base soft and dipping deeply into the mucosa; along the inferior surface of the ulcer the opening was found, indicating the point of perforation. In placing the esophagus in its normal position an almost complete obstruction was presented at the point of stricture. Microscopically, the mass was found to be an adenocarcinoma.

The case is interesting as showing one of the rather rare results of rupture produced by instrumentation in a carcinomatous growth of the esophagus.

CASE II.—*Carcinoma of the Esophagus with Perforation into the Right Lung and the Production of Pneumonia and Abscess; Spontaneous Cure of the Lung Abscess with Fatal Termination from the*

Cancer. J. S., female, aged sixty-nine years, consulted us on September 1, 1920, complaining of difficulty in swallowing. The family history is unimportant. The past history is also negative, the patient never having been ill before the onset of the present affection, excepting for the suggestion of some apparent gall-bladder attacks several years previously. She has always enjoyed a good digestion, the bowels moving regularly once daily, and the appetite has always been normal. The patient dates the onset of her present illness to six years back, when she had several attacks of abdominal discomfort with pressure around the heart and dyspnea. These required hypodermics of morphine for relief. She continued on fairly well for several years, except for the appearance at infrequent intervals of similar attacks, which were milder in character and readily relieved by the administration of soda and hot water. Three months before the patient consulted us she began to experience, on the swallowing of solid food, a sensation of weight and pressure in her chest. The dysphagia was soon followed by regurgitation and gradually solids were excluded from the dietary; but soon liquids, too, began to create the same difficulty. These symptoms grew progressively worse; anorexia appeared, very little food was ingested and marked loss of weight ensued.

The physical examination made at this time revealed practically normal findings. The abdomen appeared normal; no enlargements or tender areas were noted. On attempting to pass a stomach tube, however, a definite resistance was encountered at about 7 inches from the incisor teeth, and on extracting the tube some blood was observed on the tip end. A roentgenographical examination revealed the following findings: A definite obstruction of esophagus at the level of the fourth rib; no irregularity at the cardiac end; heart and lungs negative; stomach on level of crest, being pulled definitely to the right upper quadrant; peristalsis hyperactive; irregularity in the pyloric region; no eighteen-hour retention; duodenal cap outline indefinite; cecal retention; hepatic flexure 4.5 cm. above the crest; colon position good.

The blood examination, including the Wassermann test, was negative. A blood-sugar tolerance test revealed a high sustained curve which is commonly noted in malignant affections of the gastro-intestinal tract. In this particular case this finding is of negligible diagnostic value, since sugar was repeatedly observed in the urine of this patient later in the course of her illness, indicating that she may have been a potential diabetic with a diminished carbohydrate tolerance even at the time when the test was made.

In view of the history and findings a diagnosis of carcinoma of the esophagus near the cardia was made; the patient was referred for radium therapy, in anticipation of which the growth was inspected by direct esophagoscopy. Subsequently, several radium applications were made with apparent clinical improvement.

Following the last examination with the esophagoscope, the patient complained of severe pain in the lower substernal region with marked dyspnea and cough. The next evening she had a temperature of 101° F., with cough and pain in the right chest. On the third day, on account of the discomfort, cough and general distress, the patient was sent to the Hebrew Hospital (October 2, 1920).

The following report of the physical examination was made at the hospital the next morning: Temperature, 101° F.; pulse, 102; respiration, 28; blood-pressure, 118/54.

General appearance: The patient is an elderly white woman, fairly well nourished, lying in bed propped up on a back-rest, and at short intervals is seized with paroxysms of coughing, which last several minutes, causing dyspnea and cyanosis. The pulse is synchronous, of fair volume and tone, somewhat irregular, an extrasystole being interposed at about every sixth beat. The heart is somewhat enlarged, the apex-beat being palpable in the fifth interspace, 8 cm. from the midsternal line. The right cardiac dulness is 5 cm. to the right and 10 cm. to the left of the midsternal line in the fourth interspace. The heart sounds are clear, but there is some arrhythmia, an extrasystole being present about every sixth beat. There is a slight suggestion of a systolic murmur at the apex, which is not transmitted to the axilla. The lungs do not show any lagging on deep inspiration, the expansion being apparently equal on both sides. There is some impairment of the percussion note over the right chest to the third rib, with definite dulness to the base in the back. The breath sounds are short and jerky, with prolonged expiration over the entire right chest, but most marked from the third rib down. Exaggerated vesicular breathing was heard over the left apex. Numerous moist crepitant rales were noted over the right chest, which persisted after coughing, and some scattered moist sounds were detected over the left base. Later on whispered pectoriloquy and cavernous breathing were observed in the right base posteriorly.

Laboratory findings: The urine repeatedly showed sugar and traces of albumin, the specific gravity ranging between 1.025 to 1.034. The blood picture was as follows on October 3, 1920: White blood cells per 1 cm., 13,700; red blood cells per 1 cm., 3,936,000; hemoglobin (Sahli), 66 per cent; color index, 0.84. Differential count: Small lymphocytes, 17.5; large lymphocytes, 3; large mononuclears, 2; transitionals, 5.5; polymorphonuclear neutrophiles, 72; eosinophiles, 0; basophiles, 0. Blood sugar on fasting stomach, 0.25; blood urea N, 16 mg. Stool: Offensive yellowish fluid; stool containing no occult blood, eggs or parasites. Sputum after a few days became purulent, foul smelling, containing no tubercle bacilli nor elastic tissue, but numerous Gram-positive diplococci. Roentgen-ray studies (October 4, 1920): Roentgen-

ray examination revealed a large area of consolidation at the right base, with cavity formation.

October 11, 1920: On swallowing an opaque meal, an obstruction at a point opposite the sixth thoracic vertebræ was noted fluoroscopically where the lumen of the esophagus became definitely narrowed and irregular. The obstruction was not complete, however, as the meal eventually trickled into the stomach. The diagnosis arrived at was cancer of the esophagus, associated with consolidation of the base of the right lung and cavitation. This examination was repeated several times, when occasionally bismuth was noted trickling into the right lung from the esophagus at the point of stricture.

The course of this case in the hospital was interesting: There was a gradual elevation of the temperature, reaching 103°F. on the third evening. This peak was maintained for three evenings with a drop of a degree or more in the early morning. There was a gradual decline for two weeks, though the septic character continued along. During the early part of this period the patient was affected with severe paroxysms of coughing, which were usually followed by the expectoration of large quantities of yellowish, purulent, foul-smelling material. Deglutition became more and more difficult, being accompanied by paroxysms of coughing. The lungs gradually cleared up, the abscess cavity entirely disappeared and the expectoration practically ceased. On account of the increasing weakness and dysphagia gastrostomy was advised. The operation was performed under local anesthesia on November 15, 1920. The patient's general condition improved somewhat, and on November 27, 1920, she left the hospital. Several weeks later, when seen, she appeared still in a good condition. The lungs were entirely clear; she was swallowing small amounts of liquids, although most of her nourishment was administered through the gastrostomy opening. Soon afterward her condition changed for the worse, and about six weeks after leaving the hospital she died. An autopsy was not permitted.

CASE III.—*Carcinoma of the Esophagus with Perforation into the Right Lower Bronchus and Bronchopneumonia followed by Death.* Mr. R. M., married, aged forty-nine years, consulted us on August 12, 1922, complaining of dysphagia. He had always enjoyed good health and had never required any medical attention. His family history is unimportant. His digestion had always been normal. The difficulty in swallowing gradually increased, and in about a month after the onset the patient was forced to limit himself to milk, raw eggs and water. There was a sensation of weight and pressure in the chest following deglutition. After a thorough examination, which included a roentgen-ray and esophagoscopical investigation, a diagnosis of carcinoma of the esophagus near the

cardia was made and the patient referred to the Kelly Sanitarium for radium therapy. The Wassermann reaction was negative. Two radiations were given with some improvement after the first treatment, but none following the second. An attempt was made to increase the lumen of the esophagus and to relieve the patient by means of an electrically heated bougie, according to the method advocated by Dean. Immediately after this procedure the patient complained of pain and a sensation of heat in his chest. Three days later he noted that the taking of food or water caused violent paroxysms of coughing. He was sent to the Union Memorial Hospital for observation and treatment on January 28, 1923. The physical examination at this time revealed a well-developed, undernourished individual, somewhat dyspneic and restless. The thorax showed an increased antero-posterior diameter and a costal angle somewhat greater than 90 degrees. The vocal fremitus was normally transmitted throughout both lungs. The percussion note was slightly hyperresonant and the breath sounds broncho-vesicular. The expiration was prolonged and there was an expiratory wheeze, especially marked over the right base. There were no rales. The heart was normal; the sounds distant but clear. Since the patient refused any further palliative measures, a consultation was held to determine the advisability of radical surgery. Before deciding this question the following fluoroscopical report was obtained: Watery mixture of barium passes freely down the esophagus to the level of the third interspace in front, where it meets an obstruction which is apparently complete. Then the barium apparently disseminates throughout the walls of the esophagus. This was watched several times and constantly it was observed that a little barium passed into the right lower bronchi. After due consideration it was decided that an operation would be utterly futile. The patient was no longer able to take any nourishment by mouth, and nutrient enemata were administered at regular intervals. He was sent home, where he was kept as comfortable as possible by hypodermic administrations of morphine. The cough was very harassing and the sputum had a fetid odor. Toward the end signs of bronchopneumonia appeared, with temperature and bloody sputum, and on February 13, 1923, the patient died.

Discussion. According to Ballin and Saltzstein, perforation of the esophagus has been reported as due to the following lesions:

A. Congenital malformations.

B. Neoplasms.

C. Aneurysms.

D. Trauma.

1. Esophageal instrumentation.
2. Surgical wounds.
3. Stab and gunshot wounds.
4. Foreign bodies.

E. Spontaneous rupture.
F. Inflammation.
1. Acute esophagitis.
2. Diverticulæ.
3. Simple or peptic ulcer.
4. Luetic ulcer.
5. Tuberculosis.

We desire in this report to limit ourselves to a brief discussion of those cases which are directly the result of instrumentation. When one considers the anatomy of the esophagus, the thin and delicate walls, the normal constrictions occurring at the entrance of the gullet, the point of crossing of the aorta, the crossing of the left bronchus and the cardia and its course, which is not that of a straight tube but following the direction of the cervical and dorsal segments of the spinal cord, it is not surprising that many cases of perforation have been noted. This is more readily conceivable when we realize that esophageal instrumentation is usually practised on patients who have swallowed some foreign substance or in whom diseased esophageal walls exist, on account of which symptoms referable to the gullet have occurred. This accident occurs more readily where the esophagus is the seat of some congenital anomaly or in the presence of an unsuspected aneurysm or diverticulum. Again, on account of the frequent stomach and duodenal instrumentation necessary, when investigating and treating patients presenting gastro-intestinal symptoms, the esophagus is rendered liable to injury and possibly to perforation. This complication is more likely to follow the use of hard instruments, such as the various bougies and the esophagoscope, rather than soft tubes.

In order to diminish the occurrence of this serious injury, certain contraindications to instrumentation must be borne in mind. Of these the most important are: (1) Water hunger and cachexia, on account of which it is best to postpone the examination until the vitality of the patient has been partly restored by means of nutrient enemata or through gastrostomy feedings; (2) severe prostration due to any cause, such as high temperature, cardiac decompensation, advanced tuberculosis, shock, etc.; (3) acute inflammatory conditions following the ingestion of caustic poisons; (4) recent hemorrhages.

Numerous cases of perforation have occurred following the careless and injudicious application of instruments. In quite a few instances rupture of the esophagus has been occasioned by means of dilatation for stricture in the hands of specialists, indicating that even with the best technic accidents may occur. A careful history, together with a thorough physical and roentgen-ray survey, should precede every instrumental examination. In the presence of esophageal diverticulæ, or where multiple strictures

exist in the same patient, a string should first be swallowed and used as a guide before bougies are passed. Esophagoscopy in such cases should be practised with particular care, and the progress of the esophagoscope should be directed slowly with gentle pressure while keeping the lumen of the gullet under the direct vision of the operator.

According to Ballin and Saltzstein, perforation may occur into the neck, great vessels, respiratory tube or into the thorax. As a consequence fistulæ may develop. If this occurs in the cervical region an esophago-cutaneous fistula results; if perforation takes place in the respiratory tract there will ensue either an esophago-tracheal, esophago-bronchial or esophago-pulmonary fistula. When it occurs directly into the pleural cavity a pyopneumothorax develops. Should the break be through the thoracic wall there will be formed a transpleural esophageal fistula, *i. e.*, a communication between the esophagus and skin by way of the pleural cavity. When perforation occurs into an aneurysm or a bloodvessel hemorrhage and death will follow immediately. In a recent publication H. M. Scoville reports a case of a white boy, aged nine years, who was fed through a nasal tube on account of unconsciousness and spasticity of his jaw muscles due to encephalitis. The tube was left *in situ* and nourishment administered regularly for about a week, when the patient suddenly developed a hemorrhage and died. At autopsy a perforation of the esophagus into an anomalous right subclavian artery was demonstrated, which was due to the traumatic erosion of the bloodvessel by the tube. Mediastinitis, pneumonia, bronchiectasis, abscess formation, peritonitis and rupture, followed by death, are some of the other complications which at times follow perforation of the esophagus.

The symptoms of perforation of the esophagus depend largely on the location of the rupture. In all instances when this condition occurs following the use of instruments, there is a sudden, severe pain referable to the region of the esophagus. If this takes place into an aneurysm hemorrhage occurs, together with the accompanying signs of shock, and usually a quick, fatal termination is included in the sequence of events. Sudden perforation into the respiratory tract is usually fatal. In those instances where the patient survives the immediate effects of the accident pneumonia, pulmonary abscesses, bronchiectasis and fistulæ may develop. Coughing and choking spells when the patient attempts to eat indicate esophago-bronchial communication. At times food particles may be expelled in the drainage from the transpleural fistulæ. When an ulcer located in the lower end of the esophagus is perforated by an instrument the signs are similar to those of a perforated gastric ulcer, that is, abdominal rigidity, respiratory distress and indications of peritonitis.

The diagnosis of instrumental esophageal perforation is usually

easily made. In our first case the operator, by his tactile sense, could feel that something had given away as he manipulated the bougie. In the second case the sudden pain in the esophageal region, followed by the development of a traumatic pneumonia and the expectoration of pus, rendered the diagnosis comparatively simple. In some instances a roentgenogram may show the barium mixture escaping from the esophagus into the thorax, which was observed in our second and third cases. Vomiting of pus and the rapid development of a pyopneumothorax are suggestive signs of perforation of the esophagus. As has already been noted, coughing and choking spells following the ingestion of food indicate respiratory involvement. In many cases food particles have appeared in the fistulous opening in the skin.

The prognosis in these conditions is usually very grave. When perforation occurs into an aneurysm or the respiratory tract the accident is usually fatal. In some instances of respiratory-tract involvement the patient may survive if the resulting complication is arrested. A pyopneumothorax may be treated by thoracotomy, and drainage and a cure effected provided the esophagus is not the seat of malignant disease. Ballin and Saltzstein report a case of spontaneous cure in a patient with pyopneumothorax, following a lobar pneumonia in which perforation occurred into the esophagus, with the formation of an esophageal fistula. Thoracotomy was performed, and subsequently ingested food particles were demonstrated in the pus discharge. The drainage tube was kept in place for a period of a year, and during the difficult first few weeks the patient was fed through a duodenal tube left *in situ;* then the fistula became sufficiently narrowed to allow most of the food to pass into the stomach. Finally, it closed entirely and perfect recovery resulted. Although this is not an instance of esophageal perforation of the type that we are having under discussion, it is quite conceivable that a similar pathological process might occur as a consequence of instrumentation.

Conclusions. We wish again to call attention to the fact that instrumental esophageal perforation is not an uncommon accident. In order to diminish the frequency of this serious complication, a careful physical history and roentgen-ray survey should precede the instrumental investigation. In the presence of diverticulæ or multiple strictures a string should be utilized as a guide in passing esophageal instruments. Finally, in utilizing the esophagoscope in such cases, the progress of the instrument should be directed with gentle pressure and the lumen of the esophagus kept under the direct vision of the operator.

A DISCUSSION OF THE ETIOLOGY OF ASTHMA IN ITS RELATIONSHIP TO THE VARIOUS SYSTEMS COMPOSING THE PULMONARY NEUROCELLULAR MECHANISM WITH THE PHYSIOLOGICAL BASIS FOR THE EMPLOYMENT OF CALCIUM IN ITS TREATMENT.

By F. M. Pottenger, M.D.,
MONROVIA, CALIF.

Introduction. Asthma has long been looked upon as a disease without an anatomical basis, due largely to the fact that it was considered to be a neurosis, and, as such, to have no pathological-anatomical changes. Recently, however, the subject has been studied anew, and after a most painstaking investigation it has been shown that asthma has apparently, as an essential pathology, a thickening of the entire bronchial wall, which at times almost obliterates the lumen of the tubes.[1] The thickened musculature and enlarged mucous glands most probably afford an instance in which anatomical changes result from an overstimulation of a physiological process, for in asthma the vagus nerve, which stimulates both the musculature and the secretory glands of the bronchi, is in a state of hyperirritability; consequently these tissues are subject to prolonged vagus action.

Studies of asthma have led investigators to approach the subject from many different angles. Early opinion considered it a pure neurosis. Some have attributed it to errors in diet without regard to any definite opinion as to the nature of such errors. This idea is much older than our present knowledge of food sensitization. Others have attributed it to reflex causes, the reflex arising in the nose, sinuses, gastro-intestinal canal, urogenital system, or, in fact, in any organ or tissue of the body whose afferent nerves are able to mediate with the pulmonary branches of the vagus. Brown[2] considers it due to an inability on the part of the patient to expire in the normal easy manner, caused by "respiratory-tract catarrh," and calls his theory the "non-passive expiration theory." The most recent suggestion, and the one which is claiming most attention today, is that of anaphylaxis. Those interested in this particular phase of the subject have found substances almost without number, to which asthmatics may become sensitized, such as pollen, horse dandruff, feathers, hair, bacteria and foods. Babcock,[3] Walker,[4] [5] Rackemann[6] [7] and Cooke[8] are among the early and ardent students of this phase of the subject. The idea of sensitization is a great advance in our etiological conception, but it must not be interpreted too narrowly. With present knowledge it surely cannot be considered as the only factor active in the production of paroxysms. Some writers are too prone to hold to

one cause and exclude all others. Asthma is not so simple as that. It must be approached from a very broad viewpoint. The underlying reacting capacity of the individual's bronchial neuromuscular mechanism must be taken into consideration as well as the exciting cause.

Cooke and Vander Veer[9] analyzed inheritance as a factor in sensitization in 504 patients in whom the family history was complete, and found that sensitization was present in one or both parents in 244 instances, making 48.4 per cent. In 76 normal persons sensitization was present in only 14.5 per cent. Comparison of these figures shows a very strong hereditary tendency to sensitization. Wolff-Eisner[10] suggested that hay-fever, which is a close ally to asthma, is due to the pollen protein acting upon a hypersensitive individual. Blackfan[11] states that the condition of hypersensitiveness may be present at birth and that those with this type of heredity are prone to asthma, eczema, urticaria and hay-fever. Scheppegrell[12] states that of 1000 cases of hay-fever analyzed 43 per cent also suffered from asthma, and comments further that the actual percentage is probably much higher because many minor paroxysms are not diagnosed. Piness[13] states that 27 per cent of his patients gave a history of positive heredity. Godall,[14] in analyzing 3502 consecutive cases of serum sickness, found a great number who responded quickly with all the symptoms of profound anaphylactic shock—just as though they had been sensitized by previous injections, although they had not been given horse serum before. A considerable number of these were asthmatics. He considers that they were born anaphylactic. In this connection, Wells[15] says that fatal anaphylaxis is practically limited to asthmatics. When all the facts are carefully weighed the argument seems strongly supported that there is something in the make-up of the asthmatic patient which makes him susceptible to the action of proteins, reflex stimulation, climatic change and physical and chemical irritants.

No study of asthma can be considered complete unless it takes into account those factors which are accountable for the paroxysms, as well as the exciting agents. The following subjects require careful consideration:

1. The susceptibility of the patient to react to causative agents: (*a*) Hyperirritability of the bronchial division of the vagus nerve, usually a general vagotonia as well; (*b*) relative increase in potassium as compared with calcium ions in the cells of the bronchi; (*c*) changes in those incretions which disturb the balance in either the nerve mechanism or the ion content of the cell and probably the colloidal phases of the cell itself, particularly the thyroid, the pituitary and parathyroids.

2. Substances to which the patient becomes sensitized—pollen, animal emanations, foods, etc.

3. Inflammation and other irritations which cause reflexes to express themselves in the pulmonary branches of the vagus, such as those arising in the nose, sinuses, gastro-intestinal tract, genital system and even the lung itself.

4. Such stimulating factors as are associated with climatic change—physical and chemical irritants.

The Relationship of Asthma to the Visceral Nerves. I became convinced several years ago that we could probably make headway in our understanding of visceral diseases by classifying the various syndromes, which present during their course, according to the manner in which they affect the two components of the vegetative nervous system.[16] The symptoms accompanying these diseases may be arranged into sympathetic and parasympathetic syndromes, according to whether the irritability of the one or the other system is in the ascendency, thus: The lack of appetite, deficient secretion in the gastro-intestinal tract and relaxed musculature, resulting in constipation during acute toxic states, constitutes a sympathetic syndrome; the rapid heart and altered blood-pressure, another; hyperchlorhydria, with increased muscle tonus in the gastro-intestinal canal, colicky pains and spastic constipation, a parasympathetic syndrome; the nasal irritation, with increased nasal and lacrimal secretion in hay-fever, another; likewise the spasm of the bronchial musculature and the increased secretion which is evident during paroxysms of asthma. The rapidity of heart action and increased respiratory effort during asthma result from the deficient oxidation, and may be looked upon as incidental symptoms and not as an integral part of the asthmatic syndrome. The same is true of emphysema. In previous discussions of asthma I called attention to the relationship which the symptoms bear to the vegetative nerves,[17] [18] but did not appreciate the part which the cells themselves take in the reaction. I endeavored, however, to emphasize the fact that a broad point of view is necessary to its understanding, as is evident from the following quotation.[18]

"Asthma is a disturbance in function. It is an increase in tonus of that portion of the parasympathetics which supplies the bronchial musculature and mucous membrane. Its causes may be as diverse as the irritants which may be applied to the nerve centers which give origin to the pulmonary fibers, or to the peripheral nerves that are in reflex relationship with them."

In the bronchi the vagus of the parasympathetic system and the sympathetics are antagonistic in action. Stimulation of the vagus causes contraction (spasm) of the bronchial musculature and an increase in bronchial secretion, while stimulation of the sympathetics relaxes the bronchial musculature and decreases the bronchial secretion.

This antagonistic relationship of these two components of the

vegetative system is definite, as may be inferred from the fact that the commonly successful method of relieving the paroxysms of asthma consists either in using remedies which will inhibit the action of the vagus or those which will cause a relative increase in the antagonistic sympathetic action. Atropine is a drug with the former action, but it cannot be given in full inhibiting doses without causing great discomfort to the patient, so it is of limited value. Adrenin has been the most successful individual remedy heretofore used against the paroxysm. Adrenin effects this result by producing the same action upon the bronchial musculature as though the sympathetic nerves were stimulated, and so tends to restore the normal sympathetic-parasympathetic balance. Its usefulness is greatly limited by the fact that its action is transitory. It will relax the spasm and give relief within a few minutes after it is injected, but its effect usually lasts only a few hours when it must be repeated. The effect of sympathetic action in relieving asthmatic paroxysms has been noted by the writer in the acute toxemias accompanying tonsillitis, influenza, pneumonia, typhoid and an exacerbation in tuberculosis. In each instance asthmatic paroxysms were in abeyance during the toxic stage of the intercurrent affection. The effect in these instances was due to the toxins stimulating the sympathetic mechanism sufficiently to inhibit the vagus and relax the spasm. This action may affect both the nerves and the ions in the peripheral tissue cells.

Relationship of Ion Content of Cells to Vegetative Nerves. In studying the cause of symptoms I have been gradually led to see that action in the neuromuscular apparatus depends to a great extent upon the condition of the body cells. The condition of the cell determines to a very remarkable extent its own action, and likewise the manner in which it will react to nerve and chemical stimuli. Under differing circumstances the cell may differ physically, that is, in the physical character of the colloids which compose it, or in its content in electrolytes, and each change alters its reactivity.[19] Among other electrolytes the body cells contain calcium, potassium and sodium in certain relative proportions. A variation in the relative amount of these various ions held by the cell alters its function in the same manner as though its nerve equilibrium were disturbed; in fact, the ion content is an essential part of the neuromuscular mechanism.

One fact which emphasizes the intimate relationship between nerve and ion content of the cell is that these electrolytes can be divided into sympathetic and parasympathetic groups in a manner similar to adrenin, ergotoxin, nicotine, atropine, pilocarpine and acetocholin. Sydney Ringer,[20] [21] [22] in 1881–1882–1883, made observations bearing upon this subject long before sympathetic and parasympathetic action was understood. Ringer, in perfecting the solution which bears his name, demonstrated the antago-

nism between the calcium and potassium ions in the cell, and pointed the way, which has been all too tardily followed, for understanding the nature of cellular action. Sodium chloride solution had proved satisfactory for the histological examination of fresh tissues and for the dilution of blood, but it failed to furnish a satisfactory medium for the study of muscular action when the organ (heart) was removed from the body circulation. Ringer found that contraction of the heart of the frog could not be carried on after removal from the body for any length of time when a saline solution, isotonic with the blood, was used for perfusion. In experimenting with different substances he added calcium and found that the heart, after it had ceased beating in saline solution, could be made to contract again, but that diastole was prolonged and imperfect. By the addition of potassium to the solution already containing calcium, he strengthened the diastole and the heart-beat forcibly in both systole and diastole. He then added sodium bicarbonate and noted that the completeness of the contraction still improved. He considered that the value of the sodium was due to its rendering the solution alkaline like the blood. Recent experiments as well as clinical application, however, show that aside from its effect as an alkalinizer, sodium produces an action similar to potassium—at least in the intestines.

Now that we better understand vegetative neurology, we can readily see that calcium in Ringer's experiments acts in harmony with sympathetic stimulation, and potassium—and to a less extent sodium—in harmony with parasympathetic (vagus) stimulation. Later Howell[23] found that the inhibitory action of the vagus upon the heart was absent without the presence of potassium in the Ringer's solution, and Howell and Duke[24] found an increase in the potassium content of Ringer-Locke's solution which had passed repeatedly through the heart of a mammal under vagus stimulation, from which experiments Howell called attention (1906) to the fact that vagus action was in some way connected with the setting-free of potassium ions.

Supplementary to the work of Howell, Zondek's[25] recent experiments are of great interest. He found that in stimulating the vagus supplying an experimental heart, and, carrying the perfusate through a second heart, he could produce the same effect in the second heart as though its own vagus were stimulated. On the other hand, stimulating the sympathetic nerves and carrying the perfusate through a second heart produced the same effect in the second heart, as though its own sympathetics were stimulated. Such experiments as those of Howell and Zondek, as well as those of many others, indicate definitely that stimulation of sympathetics and parasympathetics produces different effects upon the cells of an organ, and that they cause these cells to give out into the blood stream certain definite substances which differ according to which

system of nerves is stimulated. Clinical experience also bears this out in other tissues.

With our newer conception of physiology, biochemistry and biophysics, we must assume that nerve stimulation results in changing the cell so as to cause it to take from or give out certain substances into the blood stream. It is quite probable that this effect is partly caused by producing changes in the colloids of the cells. There is no doubt that action in body cells is associated with changes in permeability of the cell membrane and the binding more firmly or giving off of various ions.

Among other workers who have reported important studies bearing on this interesting phase of medicine may be mentioned Kraus and Zondek,[26] Abderhalden,[27] Kolm and Pick,[28] Andrus and Carter,[29] Daly and Clark,[30] Hammett,[31] Loewi[32] and Sollmann.[33] The work of these observers has established beyond doubt the interdependence of the sympathetic nerves and calcium ions in the cell on the one hand, and the parasympathetic nerves and potassium ions on the other. This is a very important contribution to the understanding of the action of the neurocellular mechanism and offers important suggestions for a better understanding of the manner in which diseases produce their effects upon the organism, and further provides certain definite principles which may be made the basis of rational therapeutic endeavor.

Altered Nerve and Cell Reactivity of the Individual Included in Etiology of Asthma. It would really seem that asthmatics belong to a particular group of individuals who possess a vegetative nervous system in which parasympathetic activity prevails. In order for such nerve status to exist there must be certain conditions in the body cells themselves. Increased parasympathetic action (vagus in asthma) presupposes a relative increase in potassium as compared with calcium ions in the cells, either an actual decrease in the calcium or an actual increase in the potassium. It is quite probable that this state of relatively increased parasympathetic-potassium activity in the cells may be partly inherited and partly acquired.

It is of interest in the discussion to understand where the reaction takes place in asthma. There is a close relationship in the reaction in asthma to that of anaphylaxis. In fact, in those cases due to protein, sensitization seems identical. The weight of evidence seems to favor the view that the principal seat of activity in anaphylaxis is in the cells themselves.[15 34] Besredka[35] was early inclined to think that the seat of the reaction was in the central nervous system, but later accepted the theory that it is in the body cells themselves. Zinsser[36] sums up this phase of the subject in the following manner:

"Limiting ourselves for the present to the phenomena of anaphylaxis in which non-cellular antigens are employed, we may safely say that the evidence furnished by the incubation time

necessary in passive anaphylaxis by the transfusion experiments of Pearce and Eisenbrey[37] and of Coca,[38] and most conclusively by the work on isolated tissue of Schultz,[39] of Dale[40] and of Weil,[41] shows conclusively that the hypersusceptible state is largely determined by a changed reaction capacity to the specific antigen on the part of the fixed tissue cells—an "allergie" which is probably due to the presence of specific antibodies in the substance of the cell protoplasm, and incidentally accounts for such effects as the skin reactions."

Hypersensitive cells during the reactive stage show change in their colloidal phases, which can be removed by desensitization. That this change in colloidal arrangement of the cells is responsible for a shifting of the ion equilibrium may be conjectured. That it is evidenced by a lessened sympathetic action, which is associated with a relative deficit in calcium ions, an increased permeability of the cell membrane and an associated hyperactivity on the part of the parasympathetic nerves is definite.

Many asthmatics suffer from other manifestations of protein hypersensitization, such as hay-fever, urticaria and eczema, and show other manifestations of hyperactivity on the part of the parasympathetic system (vagotonia), such as increased oculocardiac reflex, bradycardia, hyperchlorhydria and spastic constipation; furthermore, since many of them give a history of similar conditions in parents and grandparents and other members of the family, it is of great importance to ascertain if there is not some defect in their neurocellular mechanism—either a decrease in sympathetic irritability or a decrease in the calcium ions in the cell on the one hand, or a hyperirritability on the part of the parasympathetics or an increase in the potassium ions in the cell on the other hand—which antedates and is responsible for their becoming asthmatic. It is easy to understand how such individuals could manifest this imbalance, now in one tissue and now in another, causing hay-fever, asthma, bradycardia, hypermotility and hypersecretion in the gastro-intestinal canal, or manifestations in the skin, such as urticaria and eczema, according to the tissue involved. It is also easy to understand how those individuals who manifest this hyperirritability on the part of the neurocellular mechanism of the bronchi would respond with an asthma whenever this system was stimulated unduly, either reflexly or by such a condition as protein sensitization, or by changes in weather and climate or mechanical and chemical irritants. In the causation of this underlying condition, we must bear in mind that there are certain glands of internal secretion which bear an important relationship to calcium metabolism and the activity of the sympathetic and parasympathetic systems. Their possible part in furnishing a basis for the underlying relative hypersensitiveness of the parasympathetic-potassium mechanism must be carefully investigated.

Asthma can readily be classified on the basis of these studies as a condition in which the bronchial neurocellular mechanism reacts profoundly to stimuli which do not affect normal individuals, according to Eppinger and Hess,[42] a local vagotonia. But vagotonia, which has heretofore been considered to be a condition of hypersensitiveness of the parasympathetic nerves, of which the vagus is the largest and most widely distributed, must be given a broader definition. It becomes a condition not of the nerves alone, but of the cells acted upon as well; a condition in which the ion content of the cell is disturbed and the permeability of the cell membrane increased and in which the most evident change, according to existent knowledge, consists in a relative overbalancing of the potassium-calcium equilibrium in favor of potassium, so that a reaction on the part of the cells, at least when stimulated by the parasympathetic nerves, results in action which is beyond the bounds of physiological reaction. With present knowledge we can fix the reaction, which is recognized as the paroxysm in asthma, definitely upon the neurocellular mechanism which is associated with the vagus of the parasympathetic nervous system. We must recognize, however, that the reaction probably may be precipitated in two ways: (1) By direct action upon the cells; (2) by stimulation of the bronchial fibers of the vagus nerve.

Administration of Calcium Ions for the Relief of Asthmatic Paroxysms. In applying this knowledge of the action of the neuromuscular mechanism to asthma, the possibility of relaxing the bronchial spasm and relieving the bronchial secretion by changing the electrolytic content of the cells seemed feasible. Inasmuch as an increase in the relative amount of calcium in the cell causes the same physiological action as stimulation of the sympathetic nerves, I decided that there was important therapeutic possibilities in introducing sufficient calcium to restore the normal neurocellular equilibrium of the bronchial tissues. Not having at hand any definite way of determining how much would be required, it was decided to begin the treatment with small amounts (5 cc of a 5 per cent solution intravenously, increasing to 10 cc if necessary) and to repeat every few days, watching the effect carefully. The patients under trial were kept in bed continuously.

The calcium chloride used was in sterile ampoules containing 5 cc of a 5 per cent solution. The contents of each ampoule is equivalent to 0.25 gm. of the salt. It has been found best to inject the solution slowly, taking from four to five minutes for the 10 cc, in order to avoid mild untoward effects. At the above rate of injection a slight facial flush is noted and the patient is conscious of a feeling of warmth more pronounced in the face and in or over the abdomen. The blood-pressure rises from 5 to 10 points following an injection, but usually returns to normal within thirty minutes. The pulse-rate in asthmatics may drop 10

to 20 points per minute and persist at the lower rate for a short period.

When injected more rapidly the patient complains of a feeling of intense heat in the skin and breaks out in a profuse perspiration. There is a feeling of constriction in the throat and a feeling of nausea, persisting for upward of thirty minutes. There is also a burning sensation in the rectum. Dilatation of the pupil is questionable. One patient developed an aphonia, lasting for a few minutes.

Calcium has long been recommended by the mouth in the treatment of asthma, but apparently without any particular understanding of how it acts or what doses are necessary to produce an effect. Nor has it, as far as I am able to find, received any particular support. In looking through successive numbers of a popular year-book from 1903 to 1922 I find no reference to it; neither did I in several works on practice of medicine. It is recommended, however, in circulars sent out by commercial houses who specialize in putting up drugs for intravenous medication. I also find it recommended by Meyer and Gottlieb[43] in their work on pharmacology, but for oral administration. A recent report of its intravenous administration in the treatment of asthma comes from Kayser,[44] in which he extols its use in this and many other affections. His discussion of its action, however, fails to show its relationship to the nervous system and the ions in the peripheral cells.

Since we now know calcium to be an integral part of the cell and to be necessary to sympathetic nerve action, we have a basis for its use, founded on rational biological principles. By increasing sympathetic action in the neuromuscular mechanism of the bronchi, vagus action is depressed or inhibited, and if the action is sufficiently strong the asthmatic paroxysm is relieved. How long its action will last will have to be determined by further experience.

In asthma the action of calcium upon the cell results in the same physiological process as stimulation of the sympathetic nerves or the administration of adrenin. Adrenin heretofore has been the most successful remedy in the relief of paroxysms, but its disadvantage is that its action is of such short duration. From our present experience it is hoped that the action of calcium will be of much longer duration and that it may prove efficient in supplementing the action of adrenin and relieving the paroxysms for a longer time.

This same biological explanation serves to show how calcium exerts its beneficial effects in tuberculosis of the intestine, hayfever, acute rhinitis, serum disease and other conditions which are accompanied by syndromes of parasympathetic hyperirritability. In tuberculous enteritis it increases sympathetic action which antagonizes the vagus and so relaxes the muscular tension and relieves the pain caused by it. By its relaxing effect on the musculature of the gut it may also improve diarrhea when present.

Recently, in a case of anaphylaxis caused by the injection of horse serum, we relieved the anaphylactic phenomena by an intravenous injection of 5 cc of a 5 per cent solution. We also have been able to improve the distressing symptoms of hay-fever by it. These various uses of it substantiate its general sympathicotonic nature.

The question of dosage is one which will require considerable attention. No doubt it is an individual matter, depending upon the degree of disparity between the sympathetic and the vagus tonus in the neuromuscular mechanism of the bronchi in each case.

Case Reports. CASE I.—Mrs. J. L. S., married, housewife, aged sixty-five years, entered the Pottenger Sanatorium, November 28, 1922.

Personal History. The patient suffered an attack of "grippe" thirteen years ago. There were no complications, but the patient was a long time recovering. For the last six years the patient has suffered from "colds" which were worse during the winter season. At first these colds were not accompanied by expectoration, but since the spring of 1921 a constant bronchial trouble with expectoration has been present, and the patient has been conscious of sounds in her chest that she describes as "moaning doleful sounds." The sputum at this time was "white" in color but not frothy, and contained numerous strings of inky-black particles. In November, 1921, she had a severe cold which aggravated all symptoms, but there were no distinct wheezes or whistles. The patient made a poor recovery from this attack and was "up and down" most of the winter. Sputum now changed to a dark gray. In April, 1922, the patient suffered the first real paroxysm of asthma, which lasted several hours. Following this the patient was very weak and remained in bed for some time. There was a continued wheezing character to the respiration, and this was worse at night. Added to the continuous bronchial disturbance, a distinct asthmatic paroxysm occurred about every two to three weeks. Up to this time the patient lived in Seattle. She came to Los Angeles on October 27, 1922. The asthma grew worse and the patient says continued all the time, until entering the sanatorium. Medication prior to entering the sanatorium consisted of steam inhalations and cough mixtures.

No history of any pulmonary trouble in the family.

Physical Findings. The patient lay in bed in a semi-recumbent position. She was cyanotic. Respiration was labored and pulse was rapid. She appeared weak and in distress.

Chest Findings. The respiratory note was almost obliterated by the asthmatic squeaks which were heard throughout both lungs. Numerous mucous rales were also present and a high-grade emphysema involved both lungs. The heart outline was enlarged and the sounds weak.

Except for the changes incident to age no abnormalities of the other systems were noted.

Laboratory Findings. Sputum: December 1: 10 cc in one day; 3 tubercle bacilli in ten minutes. December 14: 20 cc in one day; 1 bacillus in ten minutes.

Urine: Negative.

Blood: Hemoglobin, 92 per cent; white blood cells, 6100.

Roentgen-ray Findings. Some scarring throughout both lungs with dense hilus shadows that contain calcified nodes; no definite evidence of active pulmonary tuberculosis.

Medication. Adrenin, 1 to 1000, was given in 10-minim doses as needed to relieve the paroxysm. One dose per day was usually sufficient; occasionally two doses were given. The last dose of adrenin was administered sixteen days after entry. A total of twenty doses of 10 minims each were given. Calcium chloride (5 per cent in 5-cc doses) was given intravenously, starting November 29, and repeated every two to three days until three doses were given; then once a week for two weeks. The last dose of calcium chloride was given on December 20, twenty-three days after entry, making a total of five doses. There was a slight return of the wheezing on February 15, 1923, and one more dose of calcium chloride was given intravenously with complete relief. No return one month later.

Other therapeutic measures used were rest in bed, strychnine sulphate, several times daily for the first month, cough mixtures, as needed, and tuberculin in graduated doses. During this time only one hypodermic of morphine was resorted to.

Present Condition. March 12, 1923: The patient has been free from symptoms, except on February 15, since December 13, 1922. She feels much better. Her appetite and general appearance are much improved; respiration is free and easy; pulse-rate has fallen from 20 to 30 beats. She coughs up very little now, except a small quantity in the morning.

CASE II.—Mrs. A. W. H., aged forty-seven years, entered the sanatorium, January 29, 1923.

Personal History. In December, 1920, she moved from Idaho to Vancouver, B. C., at which time she caught a severe cold. The cough persisted and lasted for a period of two months. The condition at this time was diagnosed as asthma. Later she moved to Spokane, and the asthma still continued and paroxysms grow worse. The attacks averaged about four or five in the twenty-four hours. Adrenin was given for the attacks and many other medicines, including an asthma powder, were also administered. From December 20 until the middle of the summer of 1921 she was hardly free from asthma at any time. After two months' relief in August, 1921, paroxysms began again. From November, 1921,

to the end of January, 1922, the patient was treated by a diet low in protein and an autogenous vaccine, with apparent benefit. In the spring of 1922 she also began the use of adrenin, taking from 2 to 5 minims at a dose, which she continued as needed until February 11, 1923. After entering the sanatorium she received doses from 3 to 8 minims each night until February 11, after which no more was necessary. She also used antispasmodics by inhalation.

Since the asthma began, with the exception of the short period in the summer of 1921, she has not been free until now. On entering the sanatorium the patient was in a very high state of nervous excitement. Her physical condition was very much reduced. The lungs were filled with whistling and squeaking rales. Marked emphysema was present. The patient was extremely dyspneic, and walked with difficulty.

Laboratory Examinations. Sputum: Twenty-four-hour quantity, 65 cc; albumin, negative; bacilli, negative.

Urine: Negative.

Blood: Hemoglobin, 85 per cent; white blood cells, 6500.

After the examination was completed patient received the first dose of calcium, 5 cc of a 5 per cent solution, on February 3, 1923. The second dose of 5 cc was given three days after, on February 6. After this dose the patient felt considerable relief. The third dose was given on February 10, and was combined with 5 cc of a 50 per cent glucose solution. The patient noticed immediate relief following this third dose, and by the second day following her expectoration had been reduced to one-half its former amount. The fourth dose of 5 per cent solution was given four days later, February 14, after which expectoration still continued to decrease.

After the second dose the asthma was reduced to one attack a day. Since February 11 the patient has been entirely free from asthma. The patient says that she is now feeling the best and freest from asthma that she has been since it began two years ago, but that she lives in fear lest it return.

Case III.—Mr. B. R., single, salesman, aged twenty years, entered the sanatorium, December 14, 1922.

Personal History. Asthma began in May, 1917, while the patient was at home in New York. The trouble was severe from the beginning and would last for months at a time. For days he would have constant wheezing and was forced to remain in bed. He was given amyl nitrite and stramonium cigarettes, but no adrenin at first. The paroxysms alternated with periods of comparative freedom for several weeks. The attacks usually preceded and lasted during inclement weather. The patient was at a tuberculosis sanatorium at Loomis, New York, for about one year, and while there was given rest treatment and, during the latter part of his stay, adrenin, hypodermatically. Of this he

received from eighteen to twenty doses of 3 to 5 minims per day. In September, 1919, he went to Albuquerque and contracted typhoid fever in October, but recovered by January, 1920. During this illness he was free from asthma. All skin tests for protein sensitization were negative. He was given sodium cacodylate, about 5 hypodermics of adrenin per day, and dietary management. He felt much better during his stay in Albuquerque than in New York.

This patient went to Colorado Springs in March, 1920. The treatment was practically the same, but the asthma was more severe. Here he was given sodium cacodylate, iodides and a vaccine prepared from sputum cultures. The skin tests repeated here were negative.

Mr. R. came to Southern California in March, 1921. The iodides, sodium cacodylate and adrenin were continued. Pituitary extract by mouth was also given, but with no appreciable effect. In spite of his condition the patient went to work in August, 1922, as a salesman, demonstrating electrical appliances. He was taught how to use adrenin himself, and carried a supply with him and administered on the average about five doses daily. After four months he was forced to quite work on account of the severity of the paroxysms, which were now almost constant, except when relieved by adrenin. Adrenin was the only medication that gave him relief and he resorted to its hypodermic use from fifteen to twenty-five times a day, taking a total of 5 to 7 cc of a 1 to 1000 solution daily. All this time the sputum was persistently negative for tubercle bacilli.

Physical Findings. Aside from signs of healed tuberculosis and findings directly connected with asthma, such as an emphysematous chest, squeaking and whistling rales, no abnormalities were noted on auscultation.

Laboratory Findings. Sputum: Quantity, 100 cc a day; negative for tubercle bacilli.

Urine: Negative.

Blood: Hemoglobin, 90 per cent; white blood cells, 12,500.

Roentgen-ray Findings. Scarring in both upper lobes with thickening of the bronchial branches throughout. Slight haziness in right apex on the level of the first interspace, indicative of an old tuberculous lesion.

Medication. On entry the patient was taking a hypodermic of adrenin every hour or two during the entire day. Intravenous medication of calcium chloride was resorted to. At first only 5 cc were given and repeated every other day. After the first ten days the interval was lengthened to four and five days with 10 cc doses and finally to one dose a week. He has received a total of fourteen doses in the first two months' treatment and is free from paroxysms. Tuberculin in graduated doses was also given. The

other medication resorted to was atropine, supplemented by morphine for a few days shortly after entry. The adrenin treatment was continued, but in decreasing number of doses, until February 21. Prior to this time he had periods of twenty-four to thirty-six hours, when no adrenin was necessary. During his stay at the sanatorium he developed an acute respiratory infection with a rise in temperature to 100° and 102° F., lasting for several days. During this time he was entirely free from asthma both in signs and symptoms.

Discussion. The three cases here detailed are not enough to bring out the many difficulties that will have to be overcome in order to establish the definite part that calcium plays in the relief of the paroxysms of asthma. They are sufficient, however, to show that calcium influences the neurocellular mechanism in the manner that is necessary to the control of such paroxysms. They offer the opportunity of discussing and illustrating the ionic control of tissues and showing its relationship to the visceral nerves in a disease which has been difficult to understand and equally difficult to treat.

These cases illustrate three different types of asthma. The first and second are types which follow attacks of bronchitis. The specific element which precipitates the paroxysms in these cases was most probably bacterial in nature. It is interesting to note that the administration of calcium relieved both the bronchial spasm and the bronchial secretion. This is what would be expected from the physiological control of these tissues, since both musculature and secreting glands are activated by the vagus nerve and inhibited by the sympathetics, with which calcium works in harmony. I was not prepared, however, to expect so prompt and rapid a reduction as occurred.

The relief of heart strain with slowing of the pulse in the first case was almost phenomenal. While stimulation of the sympathetic nerves under ordinary circumstances accelerates the pulse, under the circumstances which relieve these asthmatic paroxysms it slows it, showing that the dyspnea and rapid heart in asthma are not a part of the true asthma syndrome, but a result of the mechanical interference with respiration caused by the overstimulation of the bronchial structures which results in narrowing of the tubes. The slowing of the pulse which takes place when calcium, a sympathicotonic salt, is administered may be looked upon as affording a definite proof of favorable action upon the bronchial structures.

The third case may also be of bacterial origin, but this has not been proved from sensitization tests. The patient has never reacted to any tests administered. His paroxysms may be due to some reflex cause which still remains undetermined. Asthma can be

caused reflexly by stimuli arising in any structure in the body which is supplied by sensory nerves which mediate with the motor nerves of the pulmonary branches of the vagus thus: (1) All viscera supplied with sensory nerves by the vagus; (2) those structures in the head which are supplied by the sensory fibers of the fifth cranial nerve, for the sensory branches of the fifth mediate readily with the vagus; (3) other structures found in distant parts of the body, such as the pelvis, where afferent sensory nerves are connected by intercalated neurons which carry the impulse the entire length of the cord and mediate with the vagus. The question of finding the organ or tissue from which reflexes, capable of exerting the paroxysms of asthma, arise may offer many difficulties when no evident inflammatory process is present.

One very interesting phase of the treatment in this case was the enormous amount of adrenin which the patient had used over a long period of time. This patient was much more difficult to relieve than the others. I thought of a possibility which must always be kept in mind in connection with visceral nerve action, viz., that of reverse or transferred action.[33] Sometimes when the neurons belonging to a given system become very hypersensitive a stimulation, which, under ordinary circumstances, would act on that system and produce an action or inhibition of action in certain tissues, produces the reverse. This may be due to the neurons having reached a condition in which they can no longer respond or the stimulus being transferred to the antagonistic system. Changes in the ionic content of the cell may also be a cause of such unexpected reaction.

The fact that he responded so slowly made me think that possibly the long use of adrenin in such large quantities had so sensitized his sympathetic mechanism that when an extra stimulation of the sympathetic neuromuscular mechanism was produced by the introduction of calcium ions, instead of causing an increased sympathetic action, the neurons responded but feebly and consequently the relief was only partial. By persisting, however, we were able to give complete relief.

The suggestion in this paper have nothing to do with those aspects of the study of asthma which attempt to find the exciting causes, but represent an attempt to interpret the ultimate reactions in the body in terms of physiology, biochemistry and biophysics, so as to afford some definite concept of the departures from normal in nerve balance and ion equilibrium of the cells, which are responsible for the asthmatic paroxysm. It opens up many questions for investigation. It emphasizes strongly that in our investigations of problems in visceral neurology we must have in mind a cellular as well as a neurological concept and think in terms of the entire neurocellular mechanism.

Conclusions. 1. Bronchial asthma is a condition in which the neuromuscular mechanism of the bronchial system is in a state of hyperirritability.

2. This hyperirritability shows itself as an increased action on the part of the bronchial divisions of the vagus nerve of the parasympathetic system. According to the studies here cited, the action of the vagus depends upon the presence of potassium, and increased vagus action depends upon a preponderance of potassium ions as compared with calcium ions in the bronchial tissues.

3. Inasmuch as the activity of the vagus nerve which belongs to the parasympathetic system is antagonized by the sympathetic nerves, and inasmuch as a relative increase in the calcium ions produces the same effect as sympathetic stimulation, the administration of calcium is a rational therapeutic measure in combating asthmatic paroxysms.

4. Calcium therapy has a rational basis in other conditions which are accompanied by hyperirritability of the parasympathetic system, such as asthma, hay-fever, urticaria, serum disease, spastic colon and diarrhea.

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A CASE OF ACQUIRED CHRONIC HEMOLYTIC (ACHOLURIC) JAUNDICE, SEEN FIFTEEN YEARS AGO WITH A BLOOD-PICTURE AT THAT TIME RESEMBLING ONE OF PERNICIOUS ANEMIA.

By F. Parkes Weber, M.A., M.D., F.R.C.P.,
London, England.

Case History. The patient is a woman, now aged fifty-three years, who was first admitted to hospital under my care in January, 1908, when she was thirty-seven years of age.[1] According to the history given at that time she had been healthy until three years previously, when she commenced to look pale. About a year later she had an attack of jaundice, with pains in the right side; afterward she gradually became weaker and paler and short of breath on exertion. Menstruation became scanty, and for a time there was complete amenorrhea. She suffered from recurrent epistaxis and was troubled with coldness and numbness of the hands and feet; sometimes there was a sensation of "pins and needles" in the fingers, which would "go blue."[2]

After admission to hospital in January, 1908, the condition noted was the following: The skin and conjunctivæ were yellowish. There was no pruritus or xanthoma. The legs were edematous. The heart seemed slightly dilated, and there was a faint systolic murmur, apparently not due to valvular disease. The liver and spleen were both evenly enlarged. The liver extended two or three fingers' breadth below the ribs, and the spleen, which was hard, reached almost to the anterior-superior iliac spine. The condition of the patient's mouth was not bad, though she had lost many of her teeth. Occasionally there was slight bleeding from the gums. Attacks of epistaxis were frequent. Ophthalmoscopical examination (Dr. C. Markus) showed numerous bright red, round, retinal hemorrhages in both eyes, chiefly in the upper halves of the fundi. The urine of specific gravity 1013, contained albumin (1 per mille by Esbach's tube on admission), but no tube casts. A later note of the urine stated it to be of specific gravity about 1015, of deep orange color, free from albumin and sugar, and giving no Gmelin's reaction for bile pigment, but containing

[1] I showed the case at the Medical Society of London on April 13, 1908, February 8, 1909, and January 27, 1913 (*Trans. Med. Soc. Lond.*, 1913, **36**, 360). I also described the case in full in the Am. Jour. Med. Sci., Philadelphia, 1909, **138**, 24, and published a sequel in the *Practitioner*, London, 1913, **90**, 811. The patient was shown on May 29, 1923, at the Medical Section of the Royal Society of Medicine, London.

[2] I would here note that even more decided nervous troubles and actual combined degeneration of the spinal cord may occur not only in pernicious anemia, but also in various anemic and cachectic conditions. Salomon (*Gesellsch. f. inn. Med. u. Kinderheilk. zu Wien*, January 29, 1914) showed a man, aged thirty-two years, with hemolytic jaundice and combined degeneration of the spinal cord.

excess of urobilin. The feces were never acholic. Examination of the gastric contents after a test-breakfast (May, 1908) showed complete absence of free hydrochloric acid.

Examination of her blood on January 31, 1908, gave the following result: Hemoglobin (by Haldane's method), 18 per cent of the normal; red cells, only 900,000 in 1 cm. of blood; white corpuscles, 6000; color index, 1. The differential count of the white cells gave: Lymphocytes, 45.6 per cent; transitionals, 4.8 per cent; large mononuclears, 2.4; neutrophile polymorphonuclears, 46; eosinophiles, 0.8; mast cells, 0.4. During the count of 500 white cells Dr. A. E. Boycott saw no ordinary normoblasts, but 8 typical megaloblasts (gigantoblasts) of the pernicious anemia type and 16 smaller nucleated red cells, resembling the typical megaloblasts except in regard to their relatively small size. There were a few polychromatophilic red cells and many punctate basophilic red cells. Decided anisocytosis and poikilocytosis were present, as in pernicious anemia. The blood picture at that time was one of typical "megaloblastic degeneration"—I would prefer to say "megaloblastic regeneration" or "megaloblastic regenerative reaction"[1]—but a striking feature was the association of chronic acholuric jaundice, and the case likewise differed from pernicious anemia in regard to the enlargement of the spleen and liver. I regarded the case at first as a variety of pernicious anemia with unusual enlargement of the spleen and liver, but afterward I came to the conclusion that it was one of acquired chronic hemolytic (acholuric) jaundice, with gastric achlorhydria and a blood picture suggestive of pernicious anemia. The resistance of the patient's erythrocytes to hemolysis, as tested with graduated hypotonic sodium chloride solutions, was less than that in various healthy persons used as controls.

In the treatment of the case the arsenical preparation known as atoxyl was especially employed; but the great improvement which ultimately followed, could not with certainty be attributed to the atoxyl, as the period of the most decided improvement commenced a considerable time after the atoxyl treatment had been discontinued.

In December, 1908, the blood showed nothing abnormal beyond slight anemia. She became free from jaundice, fever and edema. The liver could no longer be felt enlarged. The retinal hemorrhages cleared up. The condition remained fairly good, and the patient was able to do ordinary work as a domestic servant. On July 17, 1911, the red cells numbered 5,330,000 to 1 cm. of blood.

Discussion. Several features of the patient's illness up to the summer of 1909 require special mention and consideration.

[1] That is to say, the blood picture of so-called "megoloblastic degeneration" must be interpreted as representing an automatic attempt at regeneration.

Abdominal Pain. At various times the patient complained of pain or tenderness in the upper part of the abdomen, sometimes in the region of the liver, sometimes associated with fever. An attack about the middle of August, 1908, was associated with vomiting and temporary increase of the icteric tinge; a short attack in December, 1908, was accompanied by a sudden rise of temperature to 103° F. Attacks of this kind are well known in hemolytic jaundice and represent temporary exacerbations of the disease. They may be mistaken for attacks of cholelithiasis, and actual gall stones have been found in some cases.

Jaundice. While under observation the patient was never deeply jaundiced, but the conjunctivæ for a long while were distinctly yellow. With the improvement in the general condition in November, 1908, the jaundice disappeared. With a single doubtful exception (during a temporary exacerbation of the jaundice), bile pigment was never present in the urine; the feces were never acholic.

Temperature. At first there were recurrent periods of moderate fever, but after September, 1908, there was hardly any fever. On December 13, 1908, a temperature of 103° F. was noted in association with abdominal pain (see back, under *abdominal pain*).

About June, 1912, the patient commenced to suffer from interstitial keratitis of the right eye, which was evidently regarded at an eye-hospital as of syphilitic origin. When seen at the end of 1912 and in the early part of 1913 she was slightly anemic, but microscopical examination of blood films showed nothing abnormal. There was no excessive fragility of the erythrocytes toward hypotonic saline solutions: The liver was apparently not enlarged. The spleen could just be felt below the costal margin. The conjunctivæ had a slight yellowish tinge and the urine (December, 1912) showed some excess of urobilin. Her blood serum on one occasion (January, 1913) gave a positive Wassermann reaction, but on two other occasions about that time it gave a negative Wassermann reaction.

On May 8, 1923, the patient was re-admitted under my care, with the history that since I last saw her in 1913 she had remained in good health until the end of 1922, when, possibly as a result of excessive work (as a monthly nurse, cook, etc.), she commenced to suffer from a feeling of weakness, a tendency to cardiac palpitation and giddiness on exertion; she had also noticed pallor and yellowness of her face. The menopause had occurred about 1921, when she was fifty-two years of age. On re-admission I find her looking obviously anemic, with light icteric coloration of her skin and sclerotics. The spleen is moderately enlarged and the liver (not very hard to palpation) reaches down to the umbilical level. The temperature is occasionally very slightly raised; pulse, 66 to 80; respiration, 16 to 20; brachial systolic blood-pressure, 115 to

140 mm. Hg. The fundi of the eyes appear normal, but there are posterior synechiæ in the right eye from earlier plastic iritis (Dr. C. Markus). The gastric contents after a test-breakfast show complete absence of free hydrochloric acid and of pepsin (achylia gastrica). The blood serum (May 10, 1923) gives a completely negative Wassermann reaction. The feces are if anything rather deeper colored than average feces. The urine is of a reddish-orange color, free from albumin, sugar and bilirubin, but showing excess of urobilin and urobilinogen. It is free from bile acids, according to surface tension estimations by Dr. J. W. McNee and Mr. E. A. B. Pritchard.

For the present blood examinations I am indebted to Dr. G. Welsch. The blood-count (May 9, 1923) gives: Erythrocytes, 1,800,000 per 1 cm. of blood; hemoglobin, 40 per cent; color index, 1.1; white cells, 6100 per 1 cm. of blood. The differential count of 300 white cells gives: Neutrophile polymorphonuclears, 74 per cent; lymphocytes, 24.5 per cent; no transitionals or large mononuclears; mast cells, 1.5 per cent; no eosinophiles. In regard to the red cells there is much anisocytosis; the macrocytes are especially numerous and show polychromatophilia and decided poikilocytosis. While making the differential count of white cells 3 nucleated red cells were observed; 2 of these were normoblasts with polychromatophilic cytoplasm, and the other was a large megaloblast with a large ("loose") nucleus and polychromatophilic cytoplasm. The resistance of the erythrocytes toward hemolysis was estimated (May 10, 1923) by adding drops of the whole blood to graduated hypotonic sodium chloride solutions. The hemolysis was found to commence with a 0.52 per cent solution and to be complete with 0.42 per cent solution. The resistance of the erythrocytes is therefore definitely below the normal standard; that is to say, their fragility is somewhat excessive, as it is in cases of congenital and acquired hemolytic jaundice.

Dr. J. W. McNee (June 1, 1923) kindly examined the blood for bilirubin and bile acids. The blood serum was yellowish and opalescent (physiological lipemia, owing to a recently taken meal). It gave a negative *direct*, but a positive *indirect* Hijmans-van den Bergh reaction for bilirubin, equivalent to $5\frac{1}{2}$ van den Bergh units (or 1 in 36,364). It was free from bile acids, according to surface tension estimations (Mr. E. A. B. Pritchard).

The case is one of hemolytic (acholuric) jaundice, apparently acquired. The old plastic iritis and interstitial keratitis in the right eye suggests that the patient may likewise have had syphilis. I have recently examined her only living child, a sailor, aged twenty-five years, who appears to be healthy and presents no signs of hemolytic jaundice or syphilis. After the birth of that son she never became pregnant again, but before his birth she now tells me that she had: (1) A female child, who died at twenty-one

months of "convulsions;" (2) a miscarriage; (3) a still-born child.

At first, in January, 1908, I temporarily mistook the case for one of pernicious anemia, and it is interesting to note that the blood picture now again (May, 1923) is of the pernicious-anemia type. In cases of congenital hemolytic jaundice poikilocytosis is usually not a feature of the blood picture, but there is generally great anisocytosis, with predominance of *apparent microcytes*. These "*microcytes*" are not true microcytes, as they are not really small; they have been shown by Naegeli and others to be only apparently small, because they have a relatively small diameter and a relatively small circumference; but, in regard to their total volume, they are really large, owing to their globular or ball-like shape ("Kugelzellen"). In some cases of hemolytic jaundice (especially acquired cases) like the present one there seems to be a tendency for the blood picture, during exacerbations of the disease, to assume the "pernicious anemia type," with poikilocytosis and megaloblasts, and with predominance of "macrocytes," instead of the ball cells ("Kugelzellen") of Naegeli.

It is possible that the patient's present exacerbation may be due to excessive work and fatigue. In regard to the injurious influence of mental strain and physical fatigue in cases of hemolytic jaundice, I may mention that one of the family (Ernest T.) of congenital hemolytic jaundice reported by Dr. Dorner and myself in 1910,[1] who was at that time twelve years of age and only slightly affected, had later on to undergo great strain as an artilleryman during the World War. Under the strain, after a considerable time, he broke down with an exacerbation of the disease. He became extremely anemic and his splenomegaly greatly increased, as Dr. J. H. Drysdale kindly showed me in St. Bartholomew's Hospital, where splenectomy was successfully performed in 1922. That patient's paternal grandfather, though jaundiced all his life, lived to seventy-six (not seventy years, as, owing to an error in copying, we stated in the account published in 1910), and both this and other published data proved that patients with hemolytic icterus may sometimes under ordinary circumstances live to a good age like normal persons, even though splenectomy is never performed.

The good results obtained by splenectomy (when successfully performed) in cases of hemolytic icterus seem to be due not only to the removal of the acknowledged hemolytic action of the spleen, but likewise to the removal of some subtle influence of the spleen on the bone-marrow in these cases, owing to which influence the bone-marrow produces abnormal erythrocytes with low resistance toward hemolysis. It is reasonable to suppose that the excessive hemolysis, caused by the presence of defective erythrocytes, leads

[1] Weber, F. Parkes and Dorner, G.: "Four Cases of Congenital Acholuric (Hemolytic) Jaundice in One Family," Lancet, London, 1910, **1**, 227.

to increased production by the bone-marrow of the defective type of erythrocytes in question — a "vicious circle," which to some extent can be "broken" by splenectomy.

Summary. A case of acquired chronic hemolytic anemia which was first seen fifteen years ago is reported together with a discussion of the injurious influence of mental strain and physical fatigue in cases of hemolytic jaundice, and the difficulty of the differential diagnosis in some cases from pernicious anemia.

THE DIAGNOSIS AND MANAGEMENT OF SUPRAVESICAL HEMATURIAS.*

By Paul W. Aschner, M.D.,

ADJUNCT ATTENDING SURGEON AND ASSISTANT IN SURGICAL PATHOLOGY, MT. SINAI HOSPITAL, NEW YORK.

(From the Surgical Service of Dr. Edwin Beer.)

It would seem hardly necessary to reiterate the importance of regarding every case of hematuria as one of grave possibilities until proven otherwise. It is surprising for how long a time a patient will pass bloody urine without attaching significance to it. It is still more surprising how often the first physician consulted will prescribe a diet and medication after a cursory general examination and urinalysis. The bleeding ceasing, as it often does of its own accord, both patient and doctor are lulled into a false sense of security.

If neoplasms of the urinary organs are to be detected early enough to improve our therapeutic results, patients with hematuria must be given the benefit of a prompt and complete urological examination. The important indication is to determine the source of the bleeding by cystoscopical observation, and, as a rule, the time to do so is when the patient is passing bloody urine. If the cause of the bleeding is in the bladder or urethra the diagnostic problem is relatively simple, but if the lesion is in the kidney or ureter the problem is frequently complex. In the latter case the actual source of the bleeding is not visible and the diagnosis must be arrived at by deduction and processes of exclusion. A certain routine had best be followed if accuracy is to be attained and errors avoided.

A careful history and physical examination may give important leads. For example, a recent attack of tonsillitis or scarlatina should make us suspect a focal infectious nephritis. A history of

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preceding attacks of renal colic not associated with hematuria suggests calculus. As the passage of blood clots, pieces of tissue, leukoplakic membrane or fibrinous exudate may cause severe colic, the occurrence of pain during the period of hematuria is not of differential value. Frequency and urgency of urination necessitate the careful exclusion of tuberculosis.

An enlarged kidney indicates hydronephrosis or tumor. Bilateral nodular renal enlargement suggests polycystic kidneys. Disease of the heart, lungs, or vessels which may cause circulatory disturbances are worthy of attention. Many other examples will suggest themselves.

In the examination of the urine, pus, casts, bacteria and tubercle bacilli in association with the blood should be carefully looked for. Epithelial and red blood cell casts indicate a nephritic origin for the hematuria. Pus may be present in cases of calculus, and always in tuberculosis and bacterial infections. But it must be remembered that the presence of nephritis, of calculus or of infection does not exclude the possibility of an associated tumor.

The cystoscopical observation of the bladder then determines whether the bloody urine is coming from one or both ureters. This point separates at once the bilateral hematurias, which have a constitutional or systemic etiology, from the unilateral hematurias which usually have a local pathological condition underlying them. The bladder itself may be perfectly normal in appearance, but in some cases lesions are present which give evidence of what sort of pathology exists in the kidney or ureter. The ureteral catheters are now introduced a short distance, and specimens are collected for microscopical examination, urea content and bacteriology. The catheters are then advanced and specimens collected at the middle and upper levels, if no obstruction is encountered. As to further methods of examination one is guided by the findings thus far obtained, and they will be considered in connection with the various groups of cases to be described.

Paroxysmal Hemoglobinuria. This rather rare disease is chiefly of interest to the internist.

It occurs more frequently in men than in women, and may occur in children. It is characterized by a prodromal period of malaise and nausea, then a chill followed by high temperature and sweating, pains in the muscles and back, itching of the skin, and at times urticaria. The urine voided during the attack, and for a few days thereafter, has a dark brown bloody color. The attack is brought on by exposure to cold and wet, and can readily be induced by immersion of the hand or foot in iced water. The disease has a luetic basis and a specific hemolysin is present in the blood, whose action was demonstrated *in vitro* by Donath and Landsteiner. The urine contains but few formed elements, the color being due to the presence of hemoglobin. Casts and leuko-

cytes may be present. Although as one would expect, the hemoglobinuria is bilateral, a case of unilateral hemoglobinuria was reported by Fleckseder.

Bilateral Hematurias Due to Nephritis. Included in this group are the cases of macroscopical hematuria in which the bleeding occurs from both kidneys simultaneously as demonstrable by cystoscopy. (The subject of unilateral nephritis will be discussed later.) Many cases of nephritis show more or less blood in the urine, particularly the acute and subacute forms, but only a few types are of interest here.

There are cases of *subacute hemorrhagic nephritis* in which hematuria is the presenting or sole symptom. This type of case is seen by the urologist because the usual manifestations of nephritis are absent. For example, a man, aged forty-six years, had bloody urine for four months. At first it was slight but it persisted and increased. There was no pain, urgency or frequency. Aside from loss of weight (10 pounds), and recently slight headache, there were no symptoms. The urine had been examined many times and nothing but blood reported. Physical examination was negative. Roentgen-ray of the urinary tract was negative. The blood-pressure was 145 systolic and 90 diastolic. Cystoscopy showed bloody efflux from both ureters and the ureteral specimens were of a uniform color at all levels on both sides. But on careful examination red blood cell casts were seen and this made the diagnosis of nephritis certain. Cultures proved sterile.

A number of interesting cases of *focal infectious nephritis with hematuria* have been observed both on the medical and urological services. They are almost exclusively of tonsillar origin, although in one case infection of the upper respiratory tract and in another furunculosis due to scabies were the exciting causes. The disease may be ushered in by a chill and fever and sore throat. In a few days the patient notices frequency, urgency and dysuria, pain in one or both flanks and the passage of bloody urine. A history of previous attacks may be elicited. In some cases the patient complains of nothing but bloody urine and it is only by close questioning and careful examination that the tonsillar origin of the trouble is detected. The cases occur chiefly in young and middle-aged individuals. A disproportion between the clinical well-being of the patient and the impairment of renal function is often observed. Thus the phenolsulphonephthalein excretion may be as low as 10 or 15 per cent, and the blood-nitrogen figures increased three or four fold. The blood-pressure too may be considerably elevated. The urine of these patients usually contains granular casts and leukocytes in addition to the blood. On cystoscopical examination the bladder may show no lesion, but in a few cases seen early in the disease punctate hemorrhages were observed in the trigone and larger submucous hemorrhages near the ureteral orifices. In most instances the same kind of urine flowed from the

two kidneys, and the output of indigo-carmine was equally delayed. *In all but two cases cultures of the ureteral specimens proved sterile.* The two exceptions were cases seen with Dr. Libman and Dr. Poll, in which an unusual amount of pus was present in the urine, with unusually severe vesical symptoms and a febrile course. Cystoscopy showed a diffuse cystitis, bilateral hemorrhagic nephritis and left-sided pyelitis due to Bacillus coli.

These cases have been treated by rest and dietetic regulation until the acute process has subsided. Tonsillectomy under local anesthesia has then been performed and with excellent results. In several cases the tonsillectomy was followed by lumbar pain and hematuria, a focal reaction seen similarly in tonsillectomy for arthritic conditions.

FURTHER METHODS OF EXAMINATION. In cases of unilateral hematuria any or all of the following methods should be employed in addition to the first cystoscopical examination.

1. Roentgen-ray examination.
2. Roentgen-ray examination with the opaque catheter and the injection of opaque media.
3. The wax-tipped catheter or bougie.
4. The use of the ureter catheter to detect an obstructing lesion, to induce or aggravate bleeding by manipulation, to collect material for histological examination.
5. Comparative functional tests.
6. Therapeutic tests.

The following causes of unilateral hematuria require consideration:

1. Trauma.
2. Calculus in the kidney or ureter.
3. Tuberculosis of the kidney and ureter.
4. Ureteritis and pyelitis cystica.
5. Stricture of the ureter.
6. Hydronephrosis.
7. Primary tumors of the ureter and kidney pelvis.
8. Tumors of the kidney parenchyma.
9. A group of various degenerative, inflammatory and vascular lesions both in and around the kidney, usually classified as cases of "essential hematuria."

Trauma. When bleeding of large proportions follows a slight injury one must bear in mind the possibility of a predisposing pathological condition. For example, a young man had been struck a blow in the left flank during a scuffle. One hour later he passed bloody urine. After three days of persistent hematuria he entered the hospital. Cystoscopy showed a left renal hematuria, and roentgen-ray showed a mass of stones in the kidney. The organ was removed and a bleeding ulcer was found due to the impaction of a sharp stone against the wall of the pelvis.

A hospital employee struck his left flank against the corner of a table. He resumed his work in a few minutes but soon afterward passed bloody urine. Cystoscopical examination gave evidence of a left hydronephrosis, which was confirmed by pyelography. The bleeding stopped in a few days.

When we consider how frequent calculus and tuberculosis of the upper urinary tract are, it is remarkable how seldom they are accompanied by macroscopical bleeding.

Calculus. A stone in the kidney or ureter may cause repeated attacks of hematuria with or without accompanying colic. The roentgen-ray will show the stone in about 90 per cent of cases. Phleboliths and calcified glands may produce confusing shadows, which must be properly identified by use of the opaque catheter and the injection of opaque media. Stereoscopical plates or two exposures on the same plate at different angles are desirable in these doubtful cases. The stones not visualized by the roentgen-ray (10 per cent) are usually uric acid stones. They may appear as negative shadows when opaque media are injected. Occasionally they may be impregnated with argyrol and thus made visible. By using a wax-tipped bougie or catheter a scratch mark may be obtained by contact with a stone. In the ureter this is a fairly reliable test, but if a stone is tucked away in a renal calyx, or covered with a fibrinous exudate the wax bulb does not always come in contact with it. Thus where a renal calculus is suspected a negative test has no value. In the ureter, however, a negative wax tip in the presence of an obstructing lesion is valuable. A positive scratch mark, with proper technic, constitutes good evidence of a calculus.

Tuberculosis. Cystoscopical observation gives much assistance in the diagnosis of this disease; tuberculous vesical ulcers, miliary tubercles at the ureteral ostium, and above all retraction and rigidity of the orifice. The cases with ureteral stenosis cause the most difficulty, for the bladder may show no lesions except the retraction of the orifice; the urine may show no bacilli; a catheter cannot pass the obstruction; and *the roentgenograms are very apt to show areas of calcification in the kidney, suggesting calculus to the unwary.* A negative test with the wax-tipped bougie passed to the obstructing lesion is valuable in excluding ureteral calculus. One may succeed in passing with the bulb, and on withdrawal it will be found deformed but not scratched. Inoculation of guinea-pigs with the ureteral specimens may clarify the diagnosis in obscure cases in which bacilli are not found in smears.

Stricture of the Ureter. This subject has been receiving increasing attention from urologists since the work of Hunner, of Baltimore, appeared. He has recently claimed that it is the cause of many unexplained hematurias and that by dilatation of the stricture the bleeding is stopped. Increased intracapsular tension, due to

pyelectasis or focal nephritis (tonsillar), may be responsible for the bleeding.

An example of this was a woman, aged thirty-two years, seen with Dr. E. Katz. For six months she had attacks of right renal colic accompanied by hematuria. There were also leukocytes in the urine. Roentgen-ray examination showed normal size, shape and position of the kidneys, and no evidence of a calculus. The first cystoscopy showed normal bladder and ureteral orifices. The

FIG. 1.—Bilateral ureterogram, showing dilatation above stricture of lower left ureter. Pain was contralateral.

right ureter was easily catheterized to the pelvis and a clear specimen obtained. The left ureter presented an impassable obstruction at 3 cm. and no flow could be obtained. The examination was repeated a week later and a No. 5 catheter could be passed 5 cm. only, but a profuse flow of urine containing blood cells and leukocytes was obtained. The function on this side was half that of the right, as determined by urea content and indigo-carmine excretion. A wax-tipped bougie passed against the face of the obstruction yielded no scratch mark. A ureteral pyelogram showed

dilated ureter, pelvis and calyces above the obstruction. Another examination was made, outlining both sides for comparison (Fig. 1). The stricture was then gradually dilated with wax bulbs and catheters up to No. 11 (Garceau catheter). All pain ceased, the urine cleared up completely. About four months later reëxamination showed a complete restoration of the left kidney and ureter to normal form and function. The patient has been well ever since.

Ureteritis and Pyelitis Cystica. Cystitis cystica is a rather uncommon disease, but well recognized by the urologist. The etiology is unknown, but it appears to be of inflammatory origin

FIG. 2.—Cross-section of ureter; autopsy specimen. Ureteritis cystica. Note tendency of mucosa to form papillomatous excrescences.

and is characterized by the presence of small cystic lesions of the mucosa, which on section are found to be inclusion cysts of the lining epithelium. Aschoff, Saltykow, Stoerck and Zuckerkandl have given excellent descriptions of the gross and microscopical pathology. The lesions may occur in any part of the bladder, but are most often seen on the trigone, about the vesical neck and the ureteral orifices. Similar lesions may be present in the mucosa of the ureters (Fig. 2) and renal pelves, and may be unilateral or bilateral. Perhaps it is the end-result of a preceding inflammatory or degenerative process.

In the ureter and pelvis it may cause obstructing masses, and there is a tendency to papilloma formation in addition. Hema-

turia from one or both sides may occur, due to secondary infection and ulceration. But there is often an associated nephritis (Fig. 3), which may in itself be responsible for the supravesical hematuria in some cases. The cystoscopical bladder picture is very characteristic, the lesions being commonly described as having a fish-eye appearance. The tropical disease of bilharzia must, however, be carefully excluded by examination of the urine for the ova of that parasite.

Four cases of this disease with associated supravesical hematuria have been observed: For example, a man, aged fifty years, was

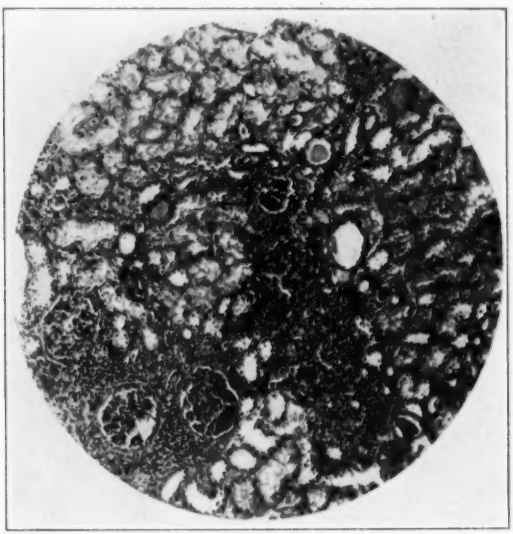

FIG. 3.—Focal nephritis in case of ureteritis and pyelitis cystica with hematuria.

admitted to the hospital, in 1919, with a history of intermittent hematuria for a year, and frequency of urination. Large areas of cystitis cystica lesions surrounded both meati and bloody urine issued from the left. The kidneys showed marked functional impairment. In 1921 he reappeared at my clinic, having been free of hematuria in the interval. The bladder showed the same lesions, but this time the blood was coming from the right ureter. Lavage of the renal pelvis with 1 per cent silver nitrate solution was followed by a cessation of bleeding.

Another patient with cystitis cystica and left-sided hematuria ceased to bleed after pyelographical examination, and a year later reported free of bleeding; but she had developed a condition of scleroderma involving the hands, feet and head.

Hydronephrosis. Without stones, and due either to congenital causes or obstructive conditions in the ureter, such as angulations, kinks and strictures, this condition may be complicated by hematuria Such bleeding may result from rupture of varices in the pelvic wall, or from an associated papillitis or nephritis. The diagnosis of this condition is readily made by cystoscopy and pyelography, but a hydronephrosis may mask a tumor of the pelvis.

Primary Tumors of the Renal Pelvis and Ureter. This is a group of cases of great importance because of difficulties attendant upon making a correct diagnosis and because of the necessity of instituting proper surgical therapy. About 150 cases of this group have been reported in the literature, and in very few has the diagnosis been made and the proper therapy instituted.

The tumors fall into three classes: Papillomas, papillary carcinomas and solid carcinomas. The papillary growths are very apt to be multiple and tend to implant themselves along the ureter and in the bladder. In some cases a diffuse papillomatosis, involving both kidneys, both ureters and the bladder, exists.

The cases present a great variety of symptoms, and may readily be confused with some of the conditions already described. The presenting features are: (1) Hematuria; (2) pain due to renal colic, chronic distention of the kidney pelvis or extension of the growth; (3) enlargement of the kidney.

For practical reasons they may be divided into two groups:

1. Cases with visible tumor.
2. Cases with no visible tumor.

Cases with Visible Tumors. A papillary tumor may be seen in the trigonal or paratrigonal area, or fine finger-like projections may form a corolla about the ureteral orifice. A pedunculated tumor may protrude from the orifice constantly or only with the efflux of urine.

If cystoscopy is done in an interval free from bleeding one is likely to attribute the bleeding to the visible growth.

If the examination is made during a period of bleeding one may be surprised to find the blood coming not from the visible tumor but with the ureteral efflux.

For example, a man, aged fifty years, with hematuria had been cystoscoped and a small papilloma near the neck of the bladder had been destroyed by fulguration. The bleeding, however, had continued. I cystoscoped him subsequently and found a bloody efflux from the left ureter. A diagnosis of papilloma of the renal pelvis was made and removal of the kidney and ureter advised. Unfortunately the patient had a cerebral accident a few days later and died. At autopsy the left kidney was found enlarged, and the upper half of the pelvis was covered with a diffuse papillomatous growth of benign character.

Cases with No Visible Tumor. These naturally offer greater difficulties in diagnosis.

A man, aged sixty-one years, a patient of Dr. Beer's, had hematuria for one year. There was a large tender right kidney. When cystoscoped in a free interval a rather large adenoma of the prostate was found. The left kidney gave normal findings. In the right ureter an impassable obstruction at 8 cm. was encountered. Roentgen-ray showed no calculus. A wax-tipped bougie gave no scratch marks. Manipulation of the catheter against the obstruction produced brisk bleeding. A subsequent examination during a period of bleeding showed a bloody efflux from the right ureter. A diagnosis of primary tumor of the ureter was made, and at operation a large hydronephrosis and hydroureter were removed. At the lower end of the ureter was a benign papilloma about an inch in diameter.

The following case illustrates how difficult it may be to discover the true cause of renal hematuria and how many confusing factors may exist in a given case. A man, aged sixty-two years, was found to be bleeding from the left kidney. The phenolsulphonephthalein excretion was 18 per cent, and the blood chemistry showed some nitrogen retention; urea nitrogen, 40; incoagulable nitrogen, 96; uric acid, 4.8; creatinin, 3.6. Pyelogram of the left kidney showed a somewhat dilated pelvis with blunted calyces. The function of this kidney was much impaired, as determined by indigo-carmine excretion. At operation a small kidney with scarred surface was found; nothing could be felt in the pelvis. The peritoneum was opened and the opposite kidney was palpated and found to be likewise contracted. The organ was, therefore, simply decapsulated and a section removed for examination. The specimen showed an advanced interstitial inflammation with destruction of tubules and atrophy of glomeruli (Fig. 4). It seemed reasonable to believe that we were dealing with a hematuria due to nephritis.

Although no further gross bleeding occurred, red blood cells continued to appear in the urine. The patient's general health remained good. About a year later an attack of hematuria brought the patient to the hospital again. On cystoscopy, I found a small papilloma protruding from the left ureteral orifice, and suspected that this was an implantation from a growth in the renal pelvis which had been overlooked at the first operation. Pyelography showed a dilated and deformed pelvis (Fig. 5). The kidney and ureter were removed by Dr. Hyman and a papillary carcinoma filling the pelvis and invading the parenchyma was found (Fig. 6).

Tumors of the Renal Parenchyma. In 50 to 70 per cent of carcinomas, sarcomas and hypernephromas of the kidney parenchyma hematuria is the first symptom. Such bleeding often lasts but a few

FIG. 4.—Specimen removed from bleeding kidney, advanced interstitial nephritis. Later proved to have tumor of renal pelvis.

FIG. 5.—Pyelogram; tumor of renal pelvis.

FIG. 6.—Microscopical section; papillary carcinoma of renal pelvis.

FIG. 7.—Pyelogram; papillary adenocarcinoma of lower pole of kidney; proven at nephrectomy.

days and may not recur for a long time. The spontaneous cessation of hemorrhage is an unfortunate occurrence because it frequently leads patient and doctor to minimize its importance. In no group of patients, therefore, is a prompt urological examination of so much importance. The tumors of the renal pelvis and ureter are likely to bleed more frequently and constantly, but the growths of the parenchyma may not manifest themselves again for a year

FIG. 8.—Pyelogram; papillary adenocarcinoma invading renal pelvis, proven at nephrectomy.

or more. In the meantime they have steadily progressed in size and have extended into the perinephritic tissues and renal vein, and when recognized have passed into an advanced and hopeless stage.

It is possible that the first bleeding occurs from dilated venules in the pelvis or uninvolved kidney tissue before the growth has actually invaded the pelvis. The pyelogram is probably the most valuable diagnostic agent in these cases, and shows a variety of deformations, displacements and filling defects (Figs. 7 and 8).

In some cases nothing can be injected into the pelvis because it is filled with blood or tumor tissue or compressed by the growth.* The induction or aggravation of bleeding by manipulating the ureter catheter in the pelvis is also of value. Occasionally tumor tissue or cells may be recovered by washing of the pelvis. The wax-tipped catheter or bougie helps exclude calculus. Functional tests will show impairment of the affected organ as compared with the healthy one. The presence of casts in the urine caused one man with hematuria to be treated for nephritis a whole year before he came to the hospital for urological examination. The bleeding was unilateral, the pyelogram showed marked deformation of the pelvis and at operation a hypernephroma of the kidney was found.

Thus far we have dealt with hematuria in which a well-defined pathology exists, although in the cases of stricture of the ureter, and of hydronephrosis the explanation of bleeding from the kidney is not so evident as in the other groups.

There are additional cases of renal hematuria which have been variously designated by writers as essential hematuria, symptomless hematuria, renal hemophilia, angioneurosis of the kidney, or "nephralgie hematurique." Rovsing spoke of mysterious renal hemorrhage and Klemperer of hematuria of the healthy kidney. These names indicate sufficiently the uncertainty as to the nature of these cases. The whole subject hinges upon this question: Should one conceive of hemorrhage from a normal kidney? Persistent efforts have been made by urologists to find a rational explanation for these cases. The result has been a progressive diminution in the number of unexplained hematurias and an increasing finesse in the study of the pathology of the affected organ. Certain difficulties present themselves, however.

1. The examination of a wedge of kidney tissue removed at operation has little value because: (*a*) If the tissue shows no lesion we cannot conclude that the entire organ is normal; (*b*) if the tissue shows an inflammatory or degenerative process we cannot conclude that this causes the bleeding. Most kidneys showing definite nephritis never bleed.

2. The examination of the whole organ removed at operation would seem to be sufficient but: (*a*) The urologist has learned that decapsulation or nephrotomy can cure these cases (as a rule, only those kidneys are removed in which the conservative operation has failed, and under such circumstances the primary condition is complicated by changes incident upon the first operation); (*b*) granted that the kidney is removed at the primary operation through error or because of the intensity of the bleeding, we cannot disregard the fact that the circulatory relations of the organ

* The use of perinephritic injection of oxygen or carbon dioxide (Carelli) may prove of assistance in demonstrating tumors of the kidney.

are disturbed in the process of its removal. Either artefacts are produced or a true vascular lesion is rendered undiscernible.

The following anatomical and pathological changes have been observed in cases of this group either on the operating table, in sections removed for study or in kidneys extirpated for hemorrhage.

1. Displacement of the kidney.
2. Abnormal mobility.
3. Perinephritis.
4. Slight hydronephrosis (pyelectasis).
5. Angioma or varix of renal papilla.
6. Incrustation of renal papilla.
7. Papillitis.
8. Bilateral nephritis with unilateral hematuria or alternating hematuria.
9. Unilateral nephritis (focal infections).

Israel, who concluded from his 14 cases that an anatomical or pathological basis always exists in renal hematuria points out that the apparent insignificance of the lesions described has caused skepticism as to their role in the production of the pronounced clinical symptoms. But, he observes, this disproportion between lesion and symptom is no more remarkable than that gross lesions can exist without producing any clinical signs.

Proof of the etiological relationship of the various lesions is offered by the results of therapy and of prolonged clinical observation.

Cases of hematuria in which nothing but abnormal motility could be demonstrated have been cured by nephropexy and some by a proper support. Cases of displacement, rotation and of fixation by adhesive perinephritis have been cured by decapsulation and nephropexy. The cause of the bleeding in these two types is a passive hyperemia or congestion due to interference with the venous return from the kidney. Moreover, it is believed by some authors (Newman, Randall, Schwyzer, Munk) that prolonged passive congestion leads to a patchy form of nephritis.

Perinephritis is to be regarded as evidence of a previous or quiescent inflammatory process.

Angioma or varix of a renal papilla was first described by Fenwick as an explanation of some cases. Cures have been effected either by resection of the papilla or by nephrotomy of the corresponding area deep enough to sever the vascular arches at the base of the pyramids. Several urologists have confirmed Fenwick's work (Pilcher, Cabot, Newman).

Incrustation of a papilla and inflammation of papillæ of the kidney have been demonstrated both macroscopically and microscopically.

Pyelectasis (mild hydronephrosis) may be present as the result of ureteral kinks in abnormally movable and displaced kidneys.

One must carefully examine for ureteral stricture in these cases. The bleeding in these instances and undoubtedly in some cases of obstructing ureteral calculus (Schwyzer) comes from the parenchyma. The improvement in drainage by ureteral dilatation, or nephropexy, and the diminution of intracapsular tension by decapsulation have resulted in cures.

The difficulties in establishing nephritis as the cause of unilateral hematuria by pathological methods have already been indicated. We have seen, however, that bilateral renal bleeding may occur in subacute hemorrhagic nephritis and in focal infectious nephritis. It is surprising that Fenwick had not observed such cases, and that Braasch thought bleeding in bilateral chronic nephritis was a terminal symptom. Israel was convinced, moreover, that unilateral hematuria occurs in cases of bilateral nephritis. This was proven by the later development of edema, cylindruria and uremia. Some of these cases were confirmed by autopsy. Many urologists and surgeons have concurred in Israel's opinion.

Payne and MacNider have studied the papillæ and the cortico-medullary zone of three bleeding kidneys which were removed. They found practically no lesions in the cortex, but there was an inflammatory fibrosis of the papillæ and cortico-medullary zones, with consequent obstruction to the venous return from the medulla and papillæ. Dilated veins in the pyramids and on the free surface of the papillæ were demonstrated as the source of the bleeding. These authors believe that an infection localized to foci in the medulla results in a fibrotic process of repair which in turn produces stasis, varicosities and hematuria.

Several cases are on record, however, notably those of Quinby, Koll and Stevens in which the kidney was removed at operation and in which careful histological study showed nothing but engorgement of the vessels between the straight collecting tubules and dilated vessels in the papillæ and beneath the pelvic epithelium. In some instances there were evidences of an inflammatory cellular and serous exudation. Two kidneys were removed at Mt. Sinai Hospital in 1914. Careful examination by the pathologist, Dr. Mandlebaum, failed to establish the cause of the bleeding.

The success of nephrotomy performed in these obscure cases of unilateral hematuria either for purposes of exploration or with a view to cure has been explained in various ways. Pilcher believed that the nephrotomy divides six main collecting veins and permanently closes them by thrombosis. Spitzer believes it is effectual only because the sutures passed to control the hemorrhage cause a partial nephrectomy.

The following cases are examples of the conditions discussed:

Case Reports, CASE I.—A traffic officer, aged forty-one years, complained of hematuria for four weeks. There were no other

urinary symptoms. Six months prior to this he had a severe cold and cough, lasting six weeks. The lower pole of the left kidney was palpable. The blood was seen coming from the left ureter. All examinations proved negative. The pyelogram showed a normal outline, but the kidney was ptosed. At operation a bulging was found on the anterior aspect near the hilum, but nephrotomy showed no gross change. The kidney was then decapsulated. The tissue excised showed marked congestion, especially of the glomeruli and a parenchymatous degeneration (Fig. 9). He has been well ever since (three years).

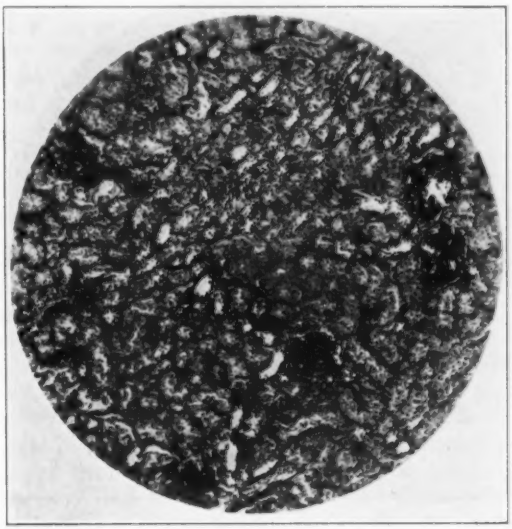

FIG. 9.—Section of renal parenchyma removed at operation in case of unilateral hematuria; congestion and parenchymatous degeneration.

CASE II.—A conductor, aged forty years, complained of hematuria for six weeks with no other symptoms. He presented a marked scoliosis to the right. The blood was coming from the left kidney. There was no disturbance in function. The kidneys appeared normal in size and shape, but were definitely displaced due to the scoliosis. Pyelogram showed no abnormality. At operation a definite perinephritis was found and depressed scars. Excised tissue showed marked congestion and areas of focal nephritis. He has remained well two years after the decapsulation of the kidney.

Case III.—A woman, aged thirty-six years, had two recent attacks of hematuria coming on after chills and fever. There was right lumbar pain radiating to the genitals. There was no difference in function between the two kidneys, but the bleeding was found to come from the right side. A pyelogram showed a dilated pelvis and calyces poorly outlined. At operation the ureter was found so thickened as to suggest tuberculosis and the kidney was removed. The specimen showed a peculiar exudative inflammation involving all the papillæ (Fig. 10), and a dilated pelvis; no other lesion.

Fig. 10.—Section of papilla in case of hematuria due to papillitis with fibrosis. Cortex showed no abnormal changes.

Case IV.—A woman, aged fifty years, had suffered with malaria for several years. For the past ten months she had intermittent attacks of hematuria with a dull ache in the left flank. The total phenolsulphonephthalein elimination was 26 per cent. The left kidney function was about half that of the right. Albumin was present in both ureteral specimens and blood in the left. Pyelogram showed a dilated pelvis, and the middle calyces not well filled. The kidneys appeared small in the roentgen-ray. At operation nothing abnormal was found except a small and somewhat contracted kidney. Nephrotomy was negative. The excised tissue showed focal nephrosclerosis. Following decapsulation and nephrotomy she remained well for several months, when hematuria recurred as vigorously as before. Dr. Beer cystoscoped the patient

and found the blood coming from the unoperated kidney (right). Here then is a definite case of bilateral focal nephrosclerosis bleeding first from one kidney and subsequently from the other.

Management of Supravesical Hematuria. Every case of hematuria should be regarded as due to neoplasm until proven otherwise. This implies an exhaustive diagnostic study of the case, using all known methods of examination.

Unilateral Hematurias. In cases of unilateral hematuria *in which all examinations have proved negative* cessation of bleeding has been effected for considerable time or permanently by various modes of treatment. Young and Kretschmer applied epinephrine through the ureteral catheter, Rytina used nitrate of silver and Barringer serum. Levy noted that distention of the pelvis in the process of pyelography frequently caused a cessation of bleeding. But no patient treated in this way should be permitted to pass out of observation, and it must be carefully explained that a recurrence of bleeding necessitates immediate reëxamination.

Cases in which pyelography shows a dilatation of the pelvis and calyces had best be suspected of neoplasm of the renal pelvis unless some other good reason can be established, such as calculus or ureteral stricture or ureteral angulation. If the pyelectasis is due to abnormal mobility and ureteral angulation a kidney support may be sufficient. If stricture has been demonstrated progressive dilatation is indicated.

In all cases with negative findings in which the simpler measures fail or in which bleeding recurs, and in all cases of unexplainable pyelectasis, nothing short of a thorough exploratory nephrotomy with inspection of the renal pelvis will meet the indications.

Decapsulation and wide nephrotomy has given good results in hematurias of nephritic origin. Varices of the papillæ may be treated similarly, but have also been cured by cauterization and papillectomy.

In tumors of the ureter and renal pelvis the operation of complete aseptic nephro-ureterectomy, as described by Beer, should be employed. Other renal tumors require nephrectomy.

The well-known principles of urological and surgical treatment are applicable to the cases of calculus and tuberculosis. Not infrequently an unsuspected calculus has been found when exploratory nephrotomy has been resorted to. A thickened ureter and increase of peripelvic fat should suggest tuberculosis to the operator.

The hematurias due to pyelitis and ureteritis cystica may be controlled by silver nitrate lavage of the pelvis and ureter. In some cases decapsulation and nephrotomy may be necessary.

Bilateral nephritic hematurias may yield to medical and dietetic treatment or to the removal of foci of infection. Bilateral decapsulation may be required in persistent cases.*

* I wish to acknowledge my indebtedness to Dr. Beer for the privilege of utilizing the material from his service, and to thank Dr. Jaches for the roentgen-ray plates.

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UNCOMPLICATED DISLOCATIONS OF THE SHOULDER: THEIR RATIONAL TREATMENT AND LATE RESULTS.

By Karl Schlaepfer, M.D.,

NEW HAVEN, CONN.

Introduction. Dislocations of the shoulder occur so frequently in the hurried life of today that the experience of a large hospital such as the surgical clinic at Zürich, Switzerland, during the last twenty years, 1899–1919, might prove helpful in bringing forth valuable suggestions with regard to the most rational treatment of these everyday accidents. From the follow-up survey of these cases, we may draw some conclusions as to the best form of therapy.

Two factors govern the treatment of any dislocation: The immobilization of the limb after proper reduction, permitting a healing of the tears in the joint capsule and resorption of the blood extravasated into the joint cavity and into the surrounding soft tissue. The second factor which combats the resulting muscular atrophy is active and passive motion to keep up the tone in the muscles, thus preventing adhesions within the joint and contractures. This second factor is partly opposed to the first one, but becomes more and more important in securing a complete restitution of function within a minimal time. The relative merit of these two factors is still a matter of controversy in the treatment of fractures and dislocations. Our survey might again arouse interest in a special group: the uncomplicated dislocation of the shoulder. Cases with complications were included in our essay insofar as the usual treatment was not interfered with.

A. General Remarks. Shoulder dislocations are the most frequent (51 to 52 per cent: Finckh) of all luxations. This is due to the marked exposure of the shoulder joint and the small articulating surface for the humerus in the shallow glenoid fossa of the scapula, necessitating its reinforcement by accessory ligaments.

This lesion occurs the most frequently in middle age: children are very seldom affected, as seen in the accompanying chart:

Age, years.	Bruns-Finckh.		Schlaepfer.		Krönlein.	
0 to 10	1		0		0	
11 to 20	2		10		2	
21 to 30	15		15		55	
31 to 40	28		16		45	
41 to 50	51		24		48	
51 to 60	71	79 per cent	21	66.6 per cent	36	50.7 per cent
61 to 70	46		22		19	
71 to 80	9		12		2	
Total	223		120		207	

The predominance of males is explained by their greater exposure to injuries in occupation, although modern traffic increases the liability to accidents of both sexes.

In our series 71 (59.1 per cent) dislocations occurred on the right side, 49 (40.8 per cent) on the left . Finckh reported 67 per cent on the right side; Körteweg in a large series found about the same frequency of occurrence on each side; Krönlein had 56 per cent left-sided lesions.

B. Forms of Dislocations. We usually distinguish between an anterior and a posterior dislocation from the respective position of the head of the humerus to the glenoid fossa of the scapula. Of our 120 cases of shoulder dislocations 113 (94 per cent) were anterior; only 7 (6 per cent) belonged to the posterior form (subspinous dis-

location). Finckh from Bruns clinic quoted among 206 luxations, 201 (92.5 per cent) anterior and 5 (2.4 per cent) posterior.

The most frequent anterior dislocation is the *subcoracoid form*, resulting from a direct pressure injury to the head of the humerus. In some cases the arm is held in hyperabduction, the greater tubercle fixed against the upper glenoid border, the surgical neck against the acromion, the head is driven through a weak place of the capsule on the anterior lower aspect. Partly by gravity, partly by muscular action the arm falls down and the head finally rests underneath the coracoid process. In exceptional cases with extensive laceration of capsule and muscle a *subclavicular form* will result. When the head becomes fixed underneath the glenoidal border we speak of a *subglenoidal* (axillary) dislocation. With the arm fixed in an elevated position, we are confronted with the *erect luxation*. In a few cases the head is driven within or underneath the subscapular muscle, thereby touching the preglenoid aspect of the scapula: *prescapular luxation*.

The posterior dislocation is very rare, the head being situated either below the acromion, the so-called *subacromial form*, or underneath the scapular spine as a *subspinous dislocation*, between the teres minor and infraspinatus muscles.

1. **Subcoracoid Dislocation**. *Frequency*. Of the 113 anterior, 108 (90 per cent) are subcoracoid and 5 (4 per cent) axillary. Gubler's recent statistics quote 111 (80 per cent) subcoracoid out of 143 cases. Da Costa mentions 75 per cent as the average for this most frequent form. Variation in the relative frequency of the different forms are due to the rules of admission governing the hospital. In a compilation including also straight ambulatory cases, omitted in our series, we obtain figures slightly different from the above.

Sex. Of our 108 *subcoracoid dislocations*, 100 occurred in males, thus demonstrating that a great number of these luxations resulted from an accident during work. The 14 (13 per cent) drunkards belong to a special group of misguided seekers of happiness. In 62 cases the right side was affected (57 per cent), in 46 the left. Gubler found 48 (43.2 per cent) on the right side and 63 (52.8 per cent) on the left. We see that the incidence of dislocations does not vary greatly on the two sides of the body.

Age, years.		
0 to 10	0	
11 to 20	10	
21 to 30	14	
31 to 40	13	
41 to 50	22	71 (66 per cent)
51 to 60	21	
Over 60	28	(61 to 70: 16)
Total	108	

In children dislocation is rather unusual. Epiphysiolysis or a fracture of the neck is more frequent. Sixty-six per cent of our cases occurred in persons over the age of forty.

Etiology. Falling on the shoulder and dislocation by direct action was responsible in the majority of our cases. This was probably the causative factor also in the 14 drunkards. In 4 cases the blow was directed from above or behind. In 5 instances the patient tried to mitigate the fall with his hand or elbow. In 1 case a sudden violent muscular action was responsible for the dislocation. In 1, a vigorous young soldier of twenty years, the dislocation occurred while throwing a camping blanket weighing 2 kilos over his shoulder. In another observation a workman, aged twenty-nine years, was lifting a heavy load of 200 kilos when he felt a sudden crack in his shoulder. Undoubtedly an abnormal condition of the capsule created a predisposition. Kaufmann quotes a subcoracoid dislocation caused by muscular action alone. Krönlein treated a woman with a dislocation acquired during an eclamptic attack. Jacquemin's patient was painting a ceiling. Baumann's patient touched an electric current with his hand, a tetanic contraction of the muscles of the shoulder girdle being responsible for the dislocation.

Diagnosis. In most of the cases the picture was a typical one, based on the changed outline of the shoulder (angulation below the acromion) and the flattening of the infraclavicular fossa. The relative fixation of the upper arm in a slightly abducted position was always characteristic. Thorough and thoughtful examination gave to the physician in almost all cases an understanding of the position of the head of the humerus, subsequently verified by roentgen-rays. The roentgen-rays have to exclude the presence of complicating fractures, not demonstrable on palpation. In cases with intensive swelling due to extreme extravasation into the soft tissues, the roentgen-rays are of the utmost value in explaining the special features of the case.

Complications. 1. *Nerve Injuries.* In a fifty-year-old drunkard a palsy of the hand, forearm and deltoid muscle was present. Anesthesia was noticed in the distribution of the ulnar nerve. No improvement was noticeable when the patient left the hospital after one month; further examination was impossible. In a second case with palsy in the distribution of the ulnar nerve, the sensory palsy subsided; but the motor disturbance persisted. Another case with complete radial (musculospiral) palsy involving also the circumflex (axillary) nerve showed a complete atrophy of the deltoid muscle after five years. The remaining muscles exhibited considerable weakness. In Gubler's compilation of 252 cases 10 (3.9 per cent) had a nerve palsy, involving generally several nerves, but clearing up gradually within a few months.

Lesions of the Bloodvessels. In most of the histories no note is made regarding the radial pulse on the two sides, although this is

a point of special importance before starting any manipulation. It should always be combined with investigation of the sensory condition of the skin, particularly in the hand. Slight changes are not often reported spontaneously by the patient. If recorded only after reduction patient may date it from the manipulations.

Fractures. In 8 (7.4 per cent) cases a *fracture of the greater tubercle* was found; in 7 instances it did not interfere with the healing. In the remaining one the loose fragment was removed by operation three days after the accident. Gubler had this complication in 7 per cent of his cases. Before the time of the roentgen-ray this complication was assumed to take place much more frequently, due to the fixing action of the supraspinatus muscle for the head of the humerus (Bardenheuer: 50 per cent). Since roentgen-rays are taken, preferably in two planes, a sagittal (antero-posterior) and a frontal (from the axilla: Iselin), this fracture is less frequently observed, mostly in older persons. Finckh had only 4 among 223 luxations. In our series of dislocations with delayed reduction we had 30 per cent, all among old people, thus justifying Bardenheuer's statistics.

Fracture of the surgical neck is mentioned in 2 cases out of 108. One was a boy, aged fourteen years, another a mail-carrier, aged fifty-one years. Gubler had 2 cases among his 252 dislocations, a male, aged sixty-five years, and a thirty-seven year old man with a temporary palsy of the circumflex and the musculospiral nerve. We had a young man, aged twenty years, with a *fracture of the acromial end of the clavicle.* Luxation of the acromial end of the clavicle, fracture of the neck of the scapula or of the coracoid process or a pertubercular fracture are complications not encountered in our case records.

Deaths. In older persons even a shoulder dislocation becomes a serious condition due to complications which may arise during the after-treatment. Three deaths occurred in this group: A man, aged seventy years, died from a pulmonary embolism three weeks after the accident, subsequent to a thrombosis of a vein of the calf. This demonstrates clearly the importance of daily active movements and massage of the lower limbs, in old persons confined to bed. A workman, aged seventy-three years, developed a lethal bronchopneumonia the day after the accident. This could possibly have been prevented by taking the patient out of bed for several hours every day or at least changing his position in bed frequently. In a housewife, aged eighty-two years, the shoulder dislocation was complicated by multiple rib fractures and fracture of the pelvis, with fatal fat embolism.

Treatment. A thorough clinical examination should precede any treatment, giving an accurate idea about the position of the head. The roentgen-rays form a truthful test and a guide for eventual complicating fractures. With Prof. Krönlein (1899 to 1911) the Schinzinger method was the method of choice for reduc-

tion in any uncomplicated case. The Kocher modification added elevation of the upper arm in a sagittal plane after its preliminary adduction to the trunk with subsequent outward rotation of the flexed forearm. This technic used formerly only in exceptional cases became in 1911, the routine procedure of Prof. Sauerbruch. Krönlein's habit was to reduce the arm without general anesthesia; a preliminary hypodermic injection of morphine, however, being usually given. Gentle manipulations were combined with an effort to divert the patient's attention from his condition. The majority of cases could be reduced successfully in this way. Kaufmann reports that out of 300 cases where he used the Kocher method in this way he had to resort to general anesthesia in only 1 per cent. In one of our observations, a subcoracoid dislocation, several attempts even under general anesthesia were fruitless. In a final trial more strength than proper was used. A sudden crack was heard. A fracture of the neck had resulted from too forcible manipulations, which are less liable to be utilized when reducing without the use of general anesthetic.

In seven instances a modified Mothe-method was applied (heel-in axilla method). Often a sudden pulling of the arm toward the contralateral pelvic brim (Riedel) proved to be successful. In 1 case a permanent extension on the dislocated humerus in a perpendicular axis, patient lying on the unaffected side did not relieve the malposition. This method (Hofmeister) is very efficacious in neglected cases, bringing about a gradual relaxation of the contracted shoulder muscles and thus rendering the difficult reduction possible.

After-treatment. From 1899 to 1911 with Prof. Krönlein the reduced arm was immobilized for one to two or three weeks in a sling (mitella). In exceptional cases the arm was fixed to the thorax by a Velpeau bandage. After this time daily massage with active and passive motion was started, increasing in degree every day. In the meantime the arm was kept in a sling for perhaps a week. With Prof. Sauerbruch the time of immobilization was shortened to a few days or at most a week. This was the technic generally accepted in all the large clinics of Europe, also by Küttner, whose results will be reviewed later.

Of our 108 cases 65 left the hospital within a few days and continued treatment in the dispensary. They all got well and did not require later readmission. Twenty left the hospital within thirty-two days with a normally movable shoulder-joint. Of the remaining 23 cases 8 were reëxamined; 7 had a perfect function. 92 (85.2 per cent) of our cases recovered with a freely movable shoulder-joint. Two of those (aged fifty-six years and forty-four years) complained of radiating pains in the shoulder when the weather was changing.

Schmidt, who treated 27 cases along the same line had 22 (81.4 per cent) cured. In the other instances the lateral elevation was par-

ticularly restricted (5 cases or 18.6 per cent). Schulz from Küttner's clinic found that from 54 patients only 7 (13 per cent) had a normal function: In 22 per cent the result was satisfactory; a restriction in the elevation of the arm and a muscular weakness persisted. Twenty-four (48 per cent) could not elevate the arm over a horizontal plane. In 65 per cent of the cases the working capacity was diminished by 20 to 30 per cent; in 10 cases even to 50 per cent. In the analysis of these cases Küttner proposed early movement as a remedy for such mediocre results.

The time necessary for healing in our series was thirty to thirty-five days. We were not able to follow up all our cases as Gubler did, whose cases were taken from the Swiss accident insurance reports. He calculated from 184 uncomplicated cases of subcoracoid dislocation, an average duration for cure of thirty-eight days; *i. e.*, when patients could resume their previous occupation without any complaint. His accurate statistics show very well that the older the patient *the longer it takes to heal* (see accompanying table):

Age, years.	Duration.			
	One month.	Two months.	Three months.	More than 3 months
0 to 20	20 (87.0 per cent)	2 (8.7 per cent)	1 (4.3 per cent)	
21 to 30	41 (87.2 per cent)	6 (12.8 per cent)		
31 to 40	19 (52.8 per cent)	17 (47.2 per cent)		
41 to 50	15 (41.7 per cent)	14 (38.0 per cent)	5 (14.0 per cent)	2 (5.5 per cent)
51 to 60	6 (30.0 per cent)	7 (35.0 per cent)	4 (20.0 per cent)	3 (15.0 per cent)
61 to 70	2 (12.5 per cent)	7 (43.7 per cent)	3 (18.8 per cent)	4 (25.0 per cent)
Over 70	.....	4 (66.6 per cent)	1 (16.2 per cent)	1 (16.2 per cent)

Körteweg who made a similar survey of cases in Holland, as did Gubler in Switzerland had an average duration of fifty-five days. The difference is partly explained by the fact that Körteweg had more cases treated in the clinic and less straight ambulatory patients.

A revolution in the treatment of shoulder dislocation was brought about in 1911 by de Marbaix's *functional method, whereby active and passive movements were instituted immediately after reduction.* Mechano-therapy, he thinks, is not as important as these movements performed daily in a very extensive way from the beginning of the treatment. With an experience of 157 cases, de Marbaix never observed a reluxation. After eighteen days of this treatment 97 per cent of the patients could resume their previous occupation. The 3 remaining cases showed a chronic arthritis (periarthritis humero-scapularis). Even this amount of active treatment could not prevent this incurable condition, whose etiology is still the center of controversy and so very unsatisfactory for any treatment.

The compilation of de Marbaix illustrates very well the ill-effect of immobilization in uncomplicated cases of shoulder dislocation:

	Average time required for healing, days.	Cases.		Remarks.
		Total.	Cured.	
Sudden extensive active mobilization	18	97	94 (97.9 per cent)	
Mobilization after *one* week	55	11	11 (100.0 per cent)	
Mobilization after *two* weeks	121	5	3	2 cases (40 per cent crippled).
Mobilization after *third* week	300	7	0	7 cases (100 per cent invalid).

The movements maintain the tone of the muscles, and facilitate the blood flow within and between the muscles, thus shortening the time necessary for the resorption of extravasated blood. Within the joint less adhesion formation with subsequent arthritic changes is possible. Küttner in reviewing his bad functional results (see Schulz) made the statement that this might be improved by the inauguration of early active and passive movements. Patients who did not return to the clinic after reduction, but assumed their duties immediately, usually showed a perfect function, supporting in this way the principles of the treatment of de Marbaix. Thiem, Kaufmann, Körteweg and Gubler became strong advocators of de Marbaix's treatment. Although the statistics prove its superiority, this method is not yet generally accepted. It may be that it is too inconsidered of the natural human feelings that follow a serious injury, especially as the movements may be somewhat painful at the beginning. The principle has to be kept in mind; slight difficulties in the details of its application according to the type of person we are dealing with, should not lead to a complete rejection of such a valuable method. Möltgen added to this method distension of the shoulder-joint by Hackenbruch clamps, to diminish the pain. He shortened the time of healing in his series to fourteen days. This is another proof of the value of the functional therapy. As de Marbaix says, this therapy applies to every form of properly reduced uncomplicated shoulder dislocation. As the subcoracoid form is the most frequent, we have discussed the treatment in connection with this most frequent luxation.

2. **Axillary Dislocations.** Only 5 (4.3 per cent) cases belong to this group, thus proving the relative infrequency of this type of dislocation. All observations concerned males of twenty, thirty, forty, forty-four and sixty-six years of age. Twice the lesion was on the right side; three times on the left.

Gubler had among 31 (21.7 per cent), 20 on the left side and 11

on the right, with an average duration of healing of forty-three days. Twenty-nine (93.5 per cent) healed completely; 2 had a permanent defect.

Two cases belonged to the erect and horizontal type of dislocations. In 1 case the arm was fixed in an elevated position (erect luxation). The other, a sixty-six year-old farmer, had his arm fixed in an abducted position of 110° (horizontal luxation). In three other observations the force was probably directed from above.

Diagnosis. The djagnosis was made in our cases by examination and confirmed by roentgen-rays. A fracture of the greater tubercle in 1 case did not interfere in any way with the usual treatment.

Treatment and After-treatment. This was the same as that outlined for the subcoracoid type.

In no case was the reduction particularly difficult. Immobilization for the first week was always instituted. Then active and passive motion, increasing daily, followed or preceded by massage, helped to bring back the function.

Late Results. Three of these 5 cases were reëxamined years after the accident. They were without any symptoms of impaired function. Two cases we lost track of.

3. **Posterior (Subspinous) Luxation.** In 7 cases observed, all were males. In all the *right* side was affected. Five were over sixty-five years of age, the other 2 about forty. In 6 out of the 7 cases a *direct* fall on the shoulder was the responsible injury; fall on the elbow was recorded in 1 patient's history.

Diagnosis. In 1 case the virtual lengthening of the upper arm was mentioned; another case seemed to have presented a shortening. In a view from the side, the axis of the humerus was directed backward with its upper end. In 1 case the arm almost touched the thorax; a relative fixation was mentioned in all except 1 record. Unfortunately the roentgen-rays of these cases were not at hand. We do not know the details of eventual complications. In an eighty-four-year-old farmer a fracture of the neck of the shoulder blade was present. This was the cause of the head of the humerus dislocating after every reduction. The patient was discharged unimproved after twenty-seven days. A woman, aged seventy-four years, had a simultaneous fracture of the posterior border of the glenoid fossa, leading to the same condition as in the preceding case. Movements were possible to a certain extent.

Death. A tailor, aged sixty-four years, died on the fourth day of double pneumonia.

Treatment. In these uncomplicated cases, reposition was effected as usual by the Kocher method without any difficulty, except in 1 case where seven unsuccessful attempts preceded the reduction. Thirty days was the average time patients were in the hospital. They were not completely cured on discharge. Changes of domicile unfortunately rendered a later examination of these cases impossible.

4. **Cases of Subcoracoid Dislocations of Delayed Reduction.** A valuable appendix to our paper is an investigation of the cases where the reduction of the subcoracoid luxation was postponed for a variable length of time. It demonstrates the importance of a thorough clinical diagnosis verified by roentgen-rays with adequate treatment and points out the complications resulting from neglect of these procedures. Of the 16 cases, 11 were male, and 5 females. Two were in the fourth decade, 5 in the sixth, 4 in the seventh and 3 in the eighth decade of life. In 5 (31 per cent) the greater tubercle was broken off, thus demonstrating the fixing action of the supraspinatus muscle for the head of the humerus. The extensive swelling setting in immediately after the injury was in these older people due to extravasation from sclerosed vessels, and the omission of roentgen-rays examination was responsible for these cases being treated as contusions of the shoulder for a variable length of time, until the persistent impairment of function urged another explanation than the reflex action of a painful contusion.

Few Days Delayed. In a carpenter, aged fifty-seven years, many maneuvers for reduction were made by different doctors in the first four days before he was sent to the hospital. After several fruitless trials the head jumped back into place by using the elevation-extension method. A concomitant fracture of the greater tubercle may have been a primary lesion or resulted from these manipulations. The final result obtained was functionally satisfactory.

A man, aged sixty-four years, was treated for contusion with compresses. After four days a roentgen-ray examination revealed the true nature of the injury. Reduction was easily performed. For two weeks the arm was bandaged to the thorax. Then passive motion was employed, the arm being in the meantime kept in a sling. No improvement being observed, a roentgenogram was taken, which showed a dislocated humerus with fracture of the surgical neck. An operation was rejected on account of the age of the patient, the chances for a functional improvement being too small. With greatly restricted mobility the patient left the hospital.

Three and a Half Weeks Delayed. A painter, aged fifty-one years, was treated for contusion during three and a half weeks, then he was referred to the hospital. After repeated fruitless attempts to reduce the subcoracoid dislocation an open reduction was performed. Ankylosis of the shoulder-joint resulted. Some motion with the scapula proved rather useful.

One Month Delayed. A smith, aged sixty-two years, fell on his shoulder. He continued to work for a day and a half; then he stopped on account of rheumatic pains. After a month he came to the hospital. Several attempts to reduce the dislocation proved unsuccessful. Finally it was reduced, and the arm kept immobile for sixteen days. Though prolonged active and passive motion

followed, the mobility remained restricted; elevation to a horizontal plane was possible. Two analogous cases were treated for rheumatism for a month. After this time following repeated attempts reduction by the abduction-elevation method was successful. The functional result in these 2 cases, which showed a fracture of the greater tubercle remained greatly impaired. A fourth uncomplicated case had the same course and result.

Five Weeks Old. Of 2 cases admitted five weeks after the injury, in 1, a woman, aged sixty-four years, reduction was possible after prolonged manipulations. The functional result was poor. In the other case, a farmer, aged seventy-four years, every attempt failed. He was discharged unimproved.

Six Weeks Old. The woman, aged sixty-two years, summoned the doctor after six weeks. By permanent extension (Hofmeister) an attempt was made to lengthen the contracted muscles around the dislocated head. This proved unsuccessful. The patient was discharged.

Two to Five Months Old. In a woman, aged sixty years, reduction was impossible after two months. Operation was contraindicated at this age. The patient complained for years of severe pains in her stiff shoulder when the weather was changing.

A woman, aged seventy-two years, and a man of the same age came three months after the injury. They were discharged unimproved, an operation being inadvisable at this age. A shoemaker, aged seventy-four years, had the same history and course.

A workman, aged forty-nine years, was operated *five* months after the accident. The wound healed *per primam;* but the motion remained greatly restricted.

In another, a laborer, aged fifty-eight years, seven months after the accident the head of the humerus was extirpated. Also in this instance the result was very unsatisfactory. Sometimes on younger individuals this operative procedure gives very good functional results.

These neglected cases illustrate very well the importance of an early accurate diagnosis controlled by roentgen-rays and subsequent rational treatment.

5. **Conclusions.** Our study shows that reduction by gentle manipulations by the Kocher method after a preliminary hypodermic injection of morphia will usually prove satisfactory. Proper reduction will be attained in the majority of cases without general anesthesia. Active and passive motion must be started immediately after reduction. No bandage is indicated. The patient should use his arm in his daily work. In a large series (157) of cases treated in this way (de Marbaix) no dislocation recurred. The time for complete cure with normal function therapy is greatly shortened (fourteen to eighteen days).

In neglected cases reduction is possible even after weeks. Finckh's

experience was that a dislocation of more than nine weeks' duration could only be treated by open reduction in the absence of any other contraindication (age). In our cases, delay in reduction always resulted in a permanent impairment of function.*

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REPORT OF SIX CASES OF CUTANEOUS ANTHRAX TREATED BY THE LOCAL AND GENERAL ADMINISTRATION OF ANTI-ANTHRAX SERUM.

By Joseph C. Regan, M.D.,

and

Catherine Regan, M.D.,

new york.

(From the Kingston Avenue Hospital, Department of Health, City of New York, Frank J. Monaghan, M.D., Commissioner of Health.)

The therapy of cutaneous anthrax has been for many years a much disputed question. The disadvantages and even dangers

* I wish to express my sincere thanks to Prof. Paul Clairmont, head of the surgical clinic at the University of Zürich for his courtesy in permitting the use of the histories of the cases.

of the measures of local treatment of malignant pustule in general use have been spoken of by one of us at length in previous articles. Suffice it to say here that these disadvantages include scarring, disfigurement, pain, the danger of secondary infection being introduced, liability of spreading the disease locally or into the circulation, prolongation of convalescence, lack of specific action and high mortality rates. The pustule is best left to its own evolution rather than to employ the more radical measures, owing to their tendency to disseminate and generalize the local disease, while the more palliative measures exert their action entirely too superficially for any direct curative effect.

The curative value of anti-anthrax serum should be regarded as established by the statistics now available. In the past the serum has in a great many cases been used in conjunction with some other measure of local treatment, which from our viewpoint was unnecessary and in many instances no doubt offset the efficacy of serum therapy. It must be remembered that anthrax in man is primarily a local infection with a decided tendency to remain as such in a high proportion of cases, and no method of treatment is warranted which tends to break down the barrier zone of the inflammatory process which Nature has so carefully and characteristically constructed in this disease. It is our belief that the local injection of serum provides a desirable means of therapy to replace the various methods that have been previously in common use, such as thermo-cautery, chemical cautery, incision, excision etc.

For the local injection, a Luer or Record syringe, 2 to 5 cc capacity, with a fine needle is used. The needle is inserted into the indurated border of the pustule just outside the eschar, and is directed fairly deeply (from 2.5 to 3.5 cm.) into the subcutaneous tissues at the base of the lesion. A total of from 6 to 12 cc of serum is injected, the needle being inserted at two or three points, and the serum given so as to circumscribe the pustule.

The injections are made once, twice and occasionally in very severe cases three times in twenty-four hours. Commonly in the usual case 4 to 6 injections suffice.

There is a slight increase in the inflammation following the first one or two local treatments, but within two or three days the lesion has usually decidedly improved, the induration and soft edema subsided, and after one week the eschar alone remains at the site of the pustule. Cultures taken after the first few injections of serum are given are almost always negative. The eschar itself spontaneously separates from the underlying tissue during the second or third week and the wound that remains quickly heals with only a minute scar, which is commonly invisible on superficial examination. The theoretical basis for the local use of serum has been discussed in the previous papers.[2, 3]

The local injection is a supplementary measure to the general (intravenous, intramuscular, and subcutaneous) administration of serum. The essential aims in giving serum being (1) to bring about a subsidence of the local lesion; (2) to counteract whatever toxemia may exist; (3) to anticipate and prevent the development of an anthrax septicemia, or to control the same if it exists when treatment is begun.

The frequency of injection, the amount of serum given and the route of administration should, we believe, be graded according to the severity of the case. Thus the serum administered varies in amount from 40 cc in mild cases every twelve to twenty-four hours to 80 to 130 cc every six to eight hours in the more severe cases with voluminous lesions. In septicemic cases the dosage is still larger, 200 to 300 cc every three to six hours intravenously. During the first twenty-four hours of treatment, while awaiting the result of blood culture, if there is any question as to the severity of the case, and if there is the least possibility of septicemia, it is best to use large doses, 100 to 150 cc, given intravenously every six to eight hours. It is now a well-recognized fact that some of the most grave types of cutaneous anthrax may have little constitutional disturbance. Probably the one factor which should guide us most in the first day's treatment is the size of the lesion and extent of the soft edema, but even this is not an invariable index of the severity of the case. Symmers,[1] in reporting the successful treatment with recovery in a septicemic case, has recently emphasized the advisability of massive dosage until the result of the blood culture is known. The writers wish most emphatically to agree with Dr. Symmers' contention in the matter. After this initial twenty-four hours of treatment and with the blood culture findings at hand, one can then follow the plan of dosage outlined in previous papers by Dr. Eichhorn and one of the writers.

The anthrax serum used in this country is that prepared by immunization along the lines suggested by Dr. Eichhorn, formerly of the Bureau of Animal Industry, Washington, D. C. Immune serum thus prepared has been shown to be more potent than the European preparations.

Anthrax serum affords the most desirable method of therapy for anthrax for several reasons. It offers the least pain; a minimum of scarring and deformity; it is applicable to all forms and locations of the malady; it is a specific measure and a safeguard against generalization of the local disease if used in time. It has on an average the lowest mortality rate and necessitates a relatively short absence from employment. Recovery occurs without any serious complications or sequels.

Two cases of cutaneous anthrax which were successfully treated by the local and general administration of anti-anthrax serum have been previously reported.[3] Subsequently in two later papers[4]

the advantages of the serum treatment of the disease as compared to the various commonly employed methods of therapy have been emphasized. The present paper includes the case reports of 6 additional patients who have recovered under local and general serum therapy; 6 other patients have also been cured, but the case histories are not included. In addition to this series of 14 successfully treated patients, we have 2, both of whom presented a septicemia on admission, and who died, 1 within twenty-four hours, the other within thirty-six hours of entrance to the hospital.

Case Reports. CASE I.—No. 3125. A young man, aged twenty-nine years, was admitted to the Kingston Avenue Hospital on December 23, 1919.

Present Illness. The first symptom observed by the patient was on December 21, when he noticed a small "pimple" on the right side of his neck. This was accompanied by slight local discomfort, weakness, malaise and later diarrhea. The lesion continued to grow larger until the time of admission to the hospital. The patient's occupation was that of a truckman and on December 17 and 18 he had been handling hides imported from China.

Physical Examination. The pustule is located on the right side of the neck in the submaxillary region, and measures 3 cm. in diameter. It consists of three zones: A central depressed cherry-black eschar, very tenacious, attached intimately to the underlying tissue, a white elevated border containing here and there a few vesicles oozing an occasional drop of serum and a red areola. Around the pustule is a hard indurated swelling measuring 6 cm. in diameter, and this in turn is surrounded by a soft edema, extending to the left side of the neck downward to the region of the trachea and upward to the lower portion of the face. The constitutional symptoms are not marked, the temperature, pulse and respiration being 100° F., 120 and 30. The heart, lungs and abdomen reveal no abnormality on examination. A blood count showed 17,000 white cells, with a differential count of 75 per cent polymorphonuclears, 23 lymphocytes and 2 large mononuclears.

Clinical Course and Treatment. December 23. On admission 38 cc of Eichhorn's anti-anthrax serum was given intramuscularly and subcutaneously in the left buttock, and 6 cc was introduced by local infiltration around the lesion, the needle being inserted at three points. December 24: The lesion is less active in appearance. There is no longer any oozing of serum from the vesicles, the induration is a little more pronounced but this is probably the result of the injection of the previous day. The general condition is improved; the temperature at 8 A.M. was 101° F., pulse 106 and respiration 28. At 10 A.M., 45 cc of anthrax serum was injected intramuscular and 8 cc of serum was given around the lesion. December 26: Pustule much improved, the inflammatory reaction surrounding

the lesion has practically disappeared as has also the blanched zone, leaving a flat black central eschar which is still intimately attached, and located in a small area of induration and edema. In the morning 32 cc of anthrax serum was given by intramuscular and subcutaneous injection and 7 cc of serum was infiltrated around the lesion. December 27: The lesion presents all the characteristics of one which is rapidly drying up, the tissues around the black central eschar having assumed a shrivelled appearance. The edema and induration are less. December 29: The lesion continues to dry up, the edema has practically entirely disappeared. The patient is able to be up out of bed. January 3: A multiform erythematous rash with slight arthritic pains, and some swelling of feet and hands has appeared and due to the serum. January 10: Eschar has spontaneously separated from the underlying tissue and with a forceps without any traction was removed. The base of the wound shows clean granulations. The edges were drawn together by adhesive plaster.

The patient was discharged on this day, and when seen two weeks later the wound had entirely healed, leaving a minute scar visible only on close inspection. The patient's general health was excellent.

Bacteriological Report. Cultures taken on admission from the serum oozing from the vesicles and by lifting up the margins of the eschar revealed a large Gram-positive bacillus, with square cut ends, occurring singly and in chains. The bacillus was non-motile. The colonies on agar plates were large dry, white, opaque with fringing projections. A few staphylococcus colonies were also present. Transplants from the large colonies gave a pure growth of anthrax bacilli showing spore formation. Inoculation of a culture into a white mouse produced death in twenty-four hours, and the same bacillus was recovered from the internal organs of the animal. In direct smears, it showed a capsule. All cultures from the lesion after the initial treatment were negative for anthrax.

Case II.—No. 1927. A man, aged forty-six years, was admitted to the Hospital on September 15, 1920. Occupation was that of longshoreman.

History. On September 11, while working, the patient began to feel tired. He returned home, and shaved, in doing which he cut off the "head of a pimple" which he noticed on the right side of his face. During the following two days his face became swollen and inflamed around the site of the "lesion." He felt rather weak, but little pain was experienced at any time. On September 13 a crust formed on the lesion. On September 14 he called a physician who gave him a solution to apply. The swelling became worse and on the following day the doctor advised him to go to the hospital.

Physical Examination. The pustule is located on the right side of the face. It consists of three zones: A cherry-red, depressed, central eschar, firm and tenacious, measuring 3 cm. x 2.5 cm., a small narrow blanched zone measuring about 3 mm. and indefinite in places, and a red areola measuring about 5 mm. Around the pustule is a zone of induration, 6 cm. in diameter in most places. This in turn merges into a soft edematous swelling extending 9 cm. on the inner side reaching to and almost entirely closing the left eye, and on the outer side extending 6 cm. involving the left auricle and mastoid process. The lesion is not especially painful and is not sensitive to touch. The examination of the chest and abdomen are negative with the exception of an impairment of the muscular quality of the first sound at the apex. The general condition is fair. The temperature is 100° F., pulse 70 and respiration 24.

Clinical Course and Treatment. On September 15, at 8 P.M., 40 cc of Eichhorn's anti-anthrax serum was injected intravenously and 8 cc subcutaneously around the pustule, the needle being inserted at three points, 1 cm. outside the eschar, in the indurated zone. At 11.25 A.M. the patient had a fairly marked chill lasting fifteen minutes, following which he perspired profusely. In the afternoon the patient was feeling so much better that he wanted to sit up in bed and read the newspaper. There was considerably less soft edema present than on the previous day. September 17, 10 A.M.: 45 cc anthrax serum given by intramuscular and subcutaneous injection also 42 cc by the intravenous route and 8 cc around the lesion. Very marked improvement in the pustule is already evident, and the edematous and indurated zones are reduced in size. The patient's general condition is excellent and temperature has reached normal. September 18: 45 cc of anthrax serum given subcutaneously and 8 cc around the lesion. The pustule is improving rapidly, the blanched zone and red areola having disappeared, the soft edema has almost entirely subsided, the indurated border is shrivelled up and is much reduced in size. September 19: 35 cc of anthrax serum injected subcutaneously. September 22: The patient is now sitting up and the lesion has an entirely different appearance, in fact all that remains is the central eschar elevated above the surrounding tissue like a button. September 30: Eschar detached from the underlying tissue by lifting it up with a forceps. The base of the wound below looks fairly clean and has almost filled up to the level of the skin with healthy granulations. October 3: Wound clean; no discharge; margins drawn together by adhesive plaster. October 6: Patient discharged, the lesion being almost healed. The wound healed within a week afterward and a minute scar visible only on careful inspection remained.

Bacteriological Report. All blood cultures were sterile. The culture of the wound taken a few hours after admission showed a

large Gram-positive bacillus corresponding in its morphological and cultural respects and its pathogenicity to the organism isolated in Case I, and therefore anthrax. All subsequent cultures taken after treatment was started were negative.

CASE III.—No. 1015. A man, aged forty-eight years, was admitted to the hospital on April 17, 1920. His occupation was that of a scaleman in warehouse for hides.

History. On April 9, while sitting beside a fire, a spark was blown onto the skin of his neck producing a small blister. The same night he shaved and in doing so cut the blister. He continued to go to work until April 16, during which time the pimple which had appeared gradually became larger and a serous fluid continually oozed from it. On April 16 he began to experience some difficulty in swallowing and felt for the first time very sick. At this time he was seen by a physician who said he had a boil. The following day he was much worse with headache, chills and perspiration, and was transferred to the Wyckoff Heights Hospital where a diagnosis of anthrax was made and 40 cc of Eichhorn's serum was administered by the intramuscular route. He was then transferred to Kingston Avenue where he was seen by Dr. Eicher and the writers.

Physical Examination. Patient is rational, but complains of pain in his neck, and states he has difficulty in swallowing and that his voice is hoarse.

On the right side of the neck about 2 inches below the angle of the jaw and on a line with the sternocleidomastoid muscle there is a large angry looking lesion, elevated above the surrounding tissue and measuring about 4.5 cm. x 3 cm., rather elongated and comprised of a central cherry-black eschar, grayish-white vesicular rim, and red areola. Puncture of the vesicular border causes a serous exudate to pour out. Around the pustule is a hard brawny swelling measuring 1 cm. at the upper and inner margins of the lesion and 3 to 5 cm. at lower and outer borders, and of an erysipelatoid appearance. Beyond this there is a soft edema extending below to the fourth rib on the right side, and posteriorly to the median line of the neck.

The chest and abdomen were negative with the exception of a faint systolic murmur at the apex. A blood count taken on admission showed a total leukocyte count of 13,300, differential: polymorphonuclears, 86 per cent; lymphocytes, 13 per cent; eosinophiles, 1 per cent. The temperature was 103° F.; pulse, 90 and respiration, 26.

Subsequent Clinical Course and Treatment. April 17: At 10.30 P.M., 26 cc of anthrax serum was injected intravenously and 6 cc of serum was given around the lesion. At 11.20 P.M., the patient had a rather severe chill with some cyanosis and lasting about

fifteen minutes. This was followed by profuse perspiration. April 18: The patient's general condition is very much improved, and the temperature is normal. He has no complaints and states that he feels much better in every way. Forty cc of serum was given subcutaneously and by intramuscular injection and 8 cc was infiltrated subcutaneously around the lesion. April 19: At 12.50 P.M., 17 cc of serum was injected intravenously and 7 cc was given around the lesion. The total leukocyte count just before the administration of serum was 13,600, while at 1.45 P.M. it was 9000, and the white cells were clumped despite thorough shaking. At 3.15 P.M. it was 16,000 and at 6.30 P.M., 12,800. April 20: 40 cc of serum was administered by the intramuscular and subcutaneous routes, and 8.5 cc by local injection. The lesion is rapidly drying up and the indurated zone and the edema are rapidly diminishing in size. April 21: The pustule is now on a level with the surrounding skin, the vesicular zone and the red inflammatory areola have disappeared leaving the dry, central reddish-black eschar with an indurated zone which has shrunken greatly, measuring now only 1.5 cm. at its widest point. The induration is of softer consistency, and has lost its red color. The soft edema is almost gone. The tumor no longer stands out on the neck as a bulging mass as it did four days ago. April 23: 20 cc of anthrax serum given by intramuscular injection. April 26: 3 cc of serum injected locally. April 28: Continued improvement. The patient has been sitting up out of bed for the last few days. Some induration has reappeared at the upper part of the lesion and a small amount of creamy pus can be pressed out of this area. A small incision was made into this superficial abscess, the pus evacuated, and packing inserted, a wet dressing of 1 per cent chlorazene being applied. April 28 to May 11: The patient is in excellent general condition, and is up and around. The wound is clearing up. May 18: The wound is entirely healed. The skin over it is of a good healthy color and there is just a slight thickening, but no scarring. May 19: The patient was discharged in excellent physical condition. He was seen subsequently at long intervals and there was no sequels from his attack and the scar left was almost invisible.

Bacteriological Report. The smears taken at the Wyckoff Heights Hospital and at Kingston Avenue Hospital on admission showed a small number of bacilli which were very large, Gram-positive, and with square cut ends, morphologically identical with anthrax. Cultures were negative after admission, but clinically the case was beyond all question one of malignant pustule and the history of exposure was clear. This was further proven by the results of treatment with anti-anthrax serum.

CASE IV.—No. 739. A man, aged twenty-seven years, was admitted to the hospital March 12, 1920.

History. The patient is employed in a brush factory in which shaving brushes are manufactured, his duties being to clean out the loose hair after the brushes are made. On March 7 he noticed a "boil" on the right side of his neck. On the following morning he consulted a physician, who advised operative interference. The boil was incised, a dressing applied and he went home. The pustule became rapidly worse and an extensive edema appeared involving the neck and lower portion of the face.

Physical Examination on Admission. The patient does not appear to be severely ill. The pustule is located on the right side of the neck just below the inferior maxilla and presents a lesion of a peculiar appearance, consisting of a central black eschar measuring about 1.5 cm. perforated in its central portion by several sieve-like openings. The eschar crust appears to cover a hollow dry cavity. Around the eschar is an indurated zone measuring about 3.5 cm. in diameter which is in turn surrounded by an area by soft edema extending upward to the right cheek and downward almost to the clavicle. The margins of the eschar are deeply adherent to the neighboring tissue and can be detached only with the greatest difficulty. A blood count taken on admission showed 11,400 leukocytes, with a differential count of 87 per cent polymorphonuclears; 12 per cent lymphocytes, and 1 per cent large mononuclears. March 12: At 9 P.M., 30 cc of anthrax serum was injected by the subcutaneous and intramuscular route. March 13: At 4 P.M., 35 cc of anthrax serum given by the same route, also 8 cc injected locally into the indurated tissues around the eschar. March 14: There is more inflammatory reaction in the pustule. The indurated area is slightly more extensive and more deeply red in color. At 5 P.M., 8 cc of serum injected locally and 30 cc intramuscular and subcutaneous. March 16: The edema around the lesion is almost entirely gone, but the induration is still present; 10 cc of serum administered by local injection. March 18: Induration still present around the lesion but the skin is becoming wrinkled. General condition of the patient is good. March 20: 8 cc of anthrax serum injected locally into the indurated margin of the eschar. March 21: Eschar crust can be loosened up at its margins, and beneath there is a profuse purulent secretion, evidently due to a secondary infection as cultures show a staphylococcus, which may have been introduced with the initial surgical incision. March 26: Lesion improving rapidly, induration and inflammation have disappeared with the exception of the right side of the wound. The eschar has spontaneously separated. March 28: The wound continues to improve the discharge becoming progressively less and the healthy granulations covering the ulcer. March 29: The margins of the wound were drawn together by adhesive and the patient was allowed to go home. The wound healed entirely within about one week after discharge, leaving a minute almost invisible scar.

Bacteriological Report. Cultures from the wound taken on admission were negative for anthrax. Yet clinically there could be no question of the diagnosis, and the inability to find the organism in the superficial portions of the pustule was no doubt due to the early surgical treatment before the case came under observation.

CASE V.—No. 2414. A man, aged thirty-three years, was admitted to the hospital on December 8, 1920, with a diagnosis of anthrax. Occupation is that of a truckman, in which work he often handles imported hides.

History. Patient noticed a small pustule on his right arm eight days before admission. He paid no attention to it until December 3, when he began to feel very ill, had chills of a severe type, one after another with high fever and delirium at intervals. These symptoms continued on the following four days the lesion meanwhile growing larger and becoming a very blue color.

Physical Examination on Entrance. The pustule is located on the palmar aspect of the forearm just below the bend of the elbow; it consists of two zones: A cherry-red-black central eschar measuring 2.5 cm. in diameter with a surrounding red elevated border. The lesion is situated in the center of a marked edematous swelling which extends on either side for almost 9 cm. General examination otherwise was negative, with the exception of a slight impairment of the myocardial element of the first sound at the apex.

Subsequent Clinical Course and Treatment. On admission the patient was seen by Dr. Charles Sherry of the resident staff and 40 cc of Eichhorn's anti-anthrax serum was given intravenously, 30 cc intramuscular and 13 cc around the lesion, cultures having been taken previously from the pustule and from the blood. December 9, at 3.30 P.M., an intravenous injection of 40 cc of the serum diluted with 60 cc of sterile physiological saline was administered. At 5 P.M. 18 cc of serum was given around the lesion. December 10: At 12.30 P.M., an intravenous injection of 25 cc of the serum in 25 cc of sterile normal saline was given, also 40 cc of serum was injected intramuscularly and subcutaneously. December 11: The lesion is little changed, the edema persists also quite some induration and a fairly marked inflammatory reaction with redness and slight pain is present for several inches around the lesion, evidently due to the serum. Wet chlorazene dressing (1 per cent) applied. Patient's general condition excellent, fever has entirely subsided and he feels fine. At 4 P.M., 50 cc of serum in 50 cc normal saline given intravenously, and 10 cc injected locally. December 13: Lesion very much improved; the inflammatory reaction due to local injections of serum has disappeared. The redness, edema and swelling have all subsided. At 11 A.M. 55 cc of serum given subcutaneously, and at 5 P.M., 75 cc in 30 cc sterile physiological saline intravenously. December 14: At 3 P.M., 50 cc of serum in

50 cc of sterile physiological saline injected by the intravenous route. December 15: 40 cc of serum by subcutaneous injection. December 16: Lesion is rapidly drying up, and very little induration remains; the tissues about the eschar have assumed a shrivelled appearance. December 21: Patient able to be up and around. December 29: Eschar has in the last few days spontaneously separated and come out; base of the wound presents healthy granulations. January 3, 1921: Edges of ulcer strapped together and patient discharged. January 17: Patient seen, wound has been healed for almost a week. There will be, if any, only a minute scar. General health excellent.

Bacteriological Report. The blood culture of December 8, while negative for growth by transplants presented on direct smears of the glucose broth a few bacilli morphologically like anthrax. The culture of the lesion taken on admission gave a pure growth of bacilli, typical in all respects of anthrax and having the same cultural characteristics and pathogenicity as that isolated in Case I. All subsequent cultures from the pustule were negative.

CASE VI.—This patient was treated by Dr. Claude Almond, formerly of the resident staff of the hospital and he has kindly consented to the inclusion of a brief reference to it in the present report.

CASE No. 2241. A young man, aged eighteen years, was admitted to the Kingston Avenue Hospital August 2, 1919, with a diagnosis of anthrax.

History. On July 26, the patient noticed a small papule just at the margin of the hair above the left eye. The swelling around the papule gradually enlarged, and by July 31 the entire left side of the face was involved. Just before the papule appeared he had used a new shaving brush which had been recently purchased.

Physical Examination. The pustule is located above the left eye, and measures 4 cm. in diameter. It has a well defined areola and two distinct vesicles at the margin of the lesion. These latter are oozing a serous fluid at intervals. There is a thick dark eschar covering the lesion and it is somewhat depressed in its center. The tissues around the pustule show some induration. There is a soft edema of the left side of the face and neck with moderate enlargement of the cervical lymph nodes.

Treatment. August 2: 20 cc of anthrax serum by intramuscular injection, 8 cc around the lesion. August 3: 20 cc anthrax serum intramuscularly, and 7 cc around the lesion. August 4: 30 cc of anthrax serum intramuscularly, and 7 cc locally injected at the base of the eschar. August 6: 20 cc of anthrax serum intramuscularly. August 6: 12 cc of anthrax serum injected locally. August 10: 28 cc of serum by the intramuscular route, and 8 cc locally.

Clinical Course. By August 4 the pustule was beginning to diminish in size and to dry up. On August 6 the induration

around the lesion had disappeared, as also had most of the soft edema. The lesion continued to improve and the eschar spontaneously separated on August 15. On August 22 the lesion had practically healed over. The patient was discharged on August 27, with no sequels, practically no scarring, and in very good condition.

Bacteriological Report. Blood cultures were negative. Cultures from the wound on admission gave a growth of large Gram-positive bacilli corresponding in all respects to those described in Case I, and evidently anthrax.

Conclusions. The local and general administration of anti-anthrax serum is the most logical, effective and specific method of treatment for cutaneous anthrax that can be employed. It possesses less objectionable features, and none of the dangers of the methods previously in common use. It may be relied on to cure every case of malignant pustule if the patient is not suffering from some chronic debilitating disease and comes under observation before septicemia has already developed. Even in the latter instance, it is the one method that offers the slightest chance of a success and therefore should always be tried.

Two cases treated by this method have been previously reported; in the present paper 6 other cases are included, all of whom recovered. We have, in addition, records of 6 more patients who were treated in a similar manner and in whom recovery ensued. This makes a total of 14 recoveries with serum therapy. We have had 2 failures in our experience, both patients coming under observation within less than forty-eight hours of death and with an anthrax septicemia already well developed on their admission to the hospital.

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SYPHILIS OF THE HEART AND BLOODVESSELS.

By Tasker Howard, M.D.
Brooklyn, N. Y.

The importance of the subject of syphilis of the heart and bloodvessels depends upon several factors: Its frequency, its high mor-

tality and the fact that, untreated, it is usually progressive, while if properly treated it may often be controlled. Its frequency is attested both at the autopsy table and in the clinic. Brooks[1] found fatal circulatory failure directly attributable to syphilis in two-thirds of 50 consecutive autopsies on syphilitic subjects. Clinically we find from 30 to 60 per cent of all cases of aortic regurgitation and practically all cases of aortic aneurysm are due to syphilis, while many cases of angina pectoris fall in the same category. The mortality of these conditions is too well known to require comment. In the study of 100 syphilitic patients from a syphilis clinic, I have found 40 per cent showing cardiac abnormalities.[2] Many of these abnormalities disappeared under treatment, particularly in the early cases. Even the more serious later involvements frequently respond very satisfactorily to specific treatment. This is not without its dangers. Routine "anti-syphilitic treatment" of these patients often ends in disaster. Wile[3] believes that the arsenical preparations are too dangerous to use at all, and advises urologists not to undertake the treatment of such patients without the coöperation of an internist. It seems to me that much of value would be lost if we discarded the use of the arsphenamine preparations entirely; but they should be used very cautiously, the dose being minimal, and the patient kept in bed and watched very carefully.

Before taking up the clinical side of the subject may I present briefly what happens to the tissues of the circulatory system in the course of a syphilitic infection? Early in the disease, there is a widespread distribution of the invading organism. At this time there is apt to be a little fever, and visible lesions due to the presence of the treponema appear on the skin and mucous membrane. But few autopsies have been performed at this stage of the disease, but it has been conclusively shown that even thus early, the offending organisms are found in the heart and aorta. Parenchymatous degeneration is seen in the muscle, and about small branches of the coronaries and vasa vasorum of the aorta there have been found little collections of lymphoid and epitheloid cells. Brooks describes perforation of the aorta through a luetic lesion at this stage (*loc. cit.*). There follows fragmentation of the muscle fibers and proliferation of the fixed connective-tissue cells with ultimate scar formation. Within the aorta such processes are said to begin in the adventitia and outer layers of the media, working toward the intima, which ultimately becomes thickened and hyaline. It is such weakened areas that give way under the pressure within the vessel and bud out into aneurysms. Involvement near the root of the aorta usually involves the aortic valve, giving rise to aortic regurgitation. The

[1] Am. Jour. Med. Sci., 1913, **146**, 513.
[2] Ibid., 1922, **163**, 64.
[3] Ibid., 1922, **164**, 415.

orifices of the coronaries are many times partially blocked with consequent myocardial degeneration of a secondary nature. The smaller vessels, as most typically seen in the brain, are the seat of perivascular infiltration, with involvement of the vessel wall, thickening, obstruction of the blood flow and formation of miliary aneurysms. These changes are usually late in their development. I have seen a tiny aneurysm of syphilitic origin in one of the retinal arteries.

Clinically, cardiac involvement may often be recognized early in the disease if it is looked for. Of 50 syphilitic patients, whom I examined during the secondary stage, 8 complained of palpitation of the heart, 5 of cardiac pain and 3 of dyspnea. One had edema. Cardiac dilatation may often be made out, and the heart is often found to be overacting, as in fever, with throbbing carotids, and possibly an occasional extrasystole. A common sign is reduplication of the second sound at the apex. Such signs mean syphilitic invasion of the myocardium and require some consideration in the treatment. It is obvious that the most important indication is the eradication of the infection, as promptly as possible, which means a vigorous course of arsphenamine and mercury. It should be remembered, however, that a full dose of arsphenamine may give a local cardiac reaction in the form of increased symptoms and it is wiser to begin with small doses, say, 0.3 gm. of the milder neoarsphenamine. Such a patient should then be decidedly limited in his activity and should be confined to bed for at least twenty-four hours after each arsphenamine injection until the cardiac symptoms have abated.

This type of case is perhaps, the most important of any, because at this stage there is every reason to believe that serious cardiac vascular syphilis may be prevented.

An example of early myocardial involvement is the case of E. M. He was a watchman, aged twenty years, who had no previous illness except mumps. Three months before admission he had developed a primary sore. About eight weeks after this he had noticed sore throat and cutaneous eruption. Shortly afterward he began to complain of precordial pain and palpitation on exertion or excitement. When I first saw him he had received five weekly injections of mercury salicylate. At this time he still showed a fading eruption on the arms and trunk and a general adenopathy. His heart extended 3 cm. to the right, 17 to the left, reaching the anterior axillary line. There was a systolic murmur at the apex, which was not transmitted until after exercise when it was louder and could be heard in the axilla. The second sound was reduplicated at the apex. There was a cardio-respiratory irregularity only, and the rate was not elevated. He showed no signs of venous stasis. With rest and continued mercurial treatment, his symptoms practically disappeared in the course of a month, and the transverse diameter decreased from 20 to 15 cm.

Perhaps the commonest and most typical cardiac lesion of syphilis is aortic regurgitation. The figures on the relative frequency with which this lesion is due to syphilitic and rheumatic infections differ considerably. In our series of 100 cases at Long Island, only 36 per cent were syphilitic. This is considerably lower than is usually given. At all events syphilitic regurgitation is a common disease. It usually is discovered years after the original infection. In fact many times the patient is quite unaware that he has syphilis. The disease may be roughly divided clinically into two stages, the first being without symptoms, or with such minor complaints as a little palpitation or throbbing in the neck and head on exertion, while the second stage is characterized by the development of dyspnea and edema. The distinction is really a very vital one, as the transition from the first to the second stage signifies, as a rule, that there has been sufficient specific involvement of the myocardium to interfere with its proper function. Specific treatment in either case may check the progressive syphilitic process, but in the case of patients in the first stage they are left with sufficient myocardial margin to meet even the increased demands of a leaky valve, while patients in the second stage have already lost their margin of safety and possibly more besides. The heart muscle does not regenerate and scar tissue is useless. The case is not altogether hopeless however, for patients who have developed symptoms. Proper rest and conservation of the muscle that they *have* left may reinstate them into the first stage, and specific treatment, by preventing further damage, offers some hope of keeping them there for a very considerable period.

To consider in some detail the treatment of these patients, let us first consider the case of a patient with a clean-cut diagnosis of syphilitic aortic insufficiency but without symptoms. His circulatory system will require no non-specific treatment; but it is of course advisable to caution him against putting undue strain upon his heart by violent exercise. The specific treatment should ultimately be as thorough as possible, but in the earlier stages it is well to remember the chances of a local reaction which may prove disastrous. I believe it is safer to begin with small doses of mercury, using from $\frac{1}{2}$ grain to $1\frac{1}{2}$ grains of one of the insoluble salts weekly by intramuscular injection. The patient should be seen two days after each injection and promptly put to bed with the first suspicion of myocardial failure. After six or eight weeks of mercury, one may turn to arsenic. Here again the danger of a reaction must be borne in mind—0.2 gm. of neoarsphenamine is quite large enough for the first dose. The patient should receive the injection in bed and stay there for twenty-four hours. If he shows no reaction the next day he may be allowed to get up. After a week the dose may be doubled. The third week a full dose may be given, if no reaction is observed, and thereafter arsphenamine

may be used as it is more potent than neoarsphenamine. No cardiac reaction is likely to be observed after this period. If a reaction is encountered while working up to the maximum dose, the patient should be kept in bed, and smaller doses used after it has passed off. When it is established that the patient tolerates specific treatment well, he should be treated like any other syphilitic with alternating courses of 6 or 8 arsphenamine injections and 8 to 12 mercury injections, or inunctions if you prefer, with periods of rest from all treatment, and attention to his general condition like any other patient. Periods of potassium iodide or mixed treatment may prove helpful. A negative Wassermann should be the goal, but of course, if it is not reached, one cannot keep up the treatment indefinitely and it is not necessary.

In fact, it is well to caution the patient at the start that the Wassermann may prove refractory, but that if he takes sufficient treatment, the Wassermann may ultimately be disregarded. If I were such a patient, I should prefer to have 5 or 6 courses of arsphenamine, with mercury in between, stretched over about three years, and would be content thereafter with an occasional course of mixed treatment.

I am afraid I can offer no illustrations of the first type that would be worth recording. Such patients are usually lost track of. The prognosis is, of course, doubtful, but it is certainly better than before we learned of the syphilitic nature of the disease. The patient is left with an aortic leak but its progressive character is at least considerably checked.

A much more difficult problem is presented in the case of a patient with syphilitic aortic regurgitation who has developed symptoms of broken compensation. The outlook is notoriously unfavorable and yet sometimes a good deal can be accomplished. Under such circumstances the specific treatment has to be postponed until the heart is doing reasonably well and even then it must be administered with the greatest caution. In the presence of dyspnea and edema, absolute rest in bed is, of course, indicated. Some form of opium is usually indispensable. Strict limitation of fluid intake will help to get rid of the edema and digitalis is of great help in slowing down and strengthening the cardiac action. If the patient can be made reasonably comfortable it is time to consider the utilization of specific medication. Under such circumstances, must we ever say, "This heart is too bad to attempt any specific treatment?" Personally, I think it is always worth the attempt, if carried out judiciously. In such cases I begin with small doses of mercury and iodide by mouth, keeping the patient in bed. The dose of the mercury can be gradually increased if well tolerated. After a month or so of this treatment, 0.1 gm. of neoarsphenamine may be given intravenously and this may be gradually increased at intervals of four days, up to 0.3 to 0.4 gm. I should hesitate to give larger

doses to a patient who had recently shown a break in compensation. The medication should be given in bed and the patient should stay there for at least twenty-four hours, being seen the next day. Throughout this period, tonic doses of digitalis should be administered and the patient should be under very strict observation. After 6 or 8 doses of neoarsphenamine, the mercury should be resumed, and may be given by inunction or the needle, but the dose should be moderate and the effect carefully watched. Such a patient requires much more restriction of activity and smaller doses throughout the course of treatment.

The outcome is certain from the start, but I believe carefully treated cases live longer than those who receive no specific medication.

May I quote the case of Mrs. A., seen first two years ago. She was thirty years old, the mother of one healthy child and did not remember ever having been sick in her life. Six months before she had had a period of pain in her left arm, attributed to neuritis. She had gradually been getting short of breath and six weeks before began to be troubled with a hard dry cough. She had recently got but little sleep because of cough and dyspnea, and for three days her legs had been swelling. She had lost 17 pounds in weight. She presented the typical signs of aortic regurgitation, with a weak, rapid heart action, the rate being 118. The lungs showed rales at the bases and her respirations were 36 to the minute. The liver was three fingers breadths below the costal margin. Her Wassermann was 4+. After four days of digitalis and codeine she was sleeping well and breathing easily, and the signs of passive congestion had largely cleared up. The codeine was needed only a few nights more, but she continued to take small doses of digitalis for months. The fourth day she was put on mixed treatment (bichloride of mercury, gr. $\frac{1}{12}$; potassium iodid, gr. 10) and this was kept up for two months, six weeks of it being spent in bed. Her general condition improved very markedly but she occasionally complained of pain the left wrist and arm and left side of the neck. She was then given 8 weekly injections of neoarsphenamine (0.1 to 0.2 gm.). This was followed by a course of mercury intramuscularly, a month's rest from treatment and three repetitions of the whole course, using gradually larger doses. She now leads a practically normal life, simply avoiding overfatigue and lying down an hour or so each day. Had she indulged in the amount of exertion which most of our hospital patients do, when they are sent home, no doubt she would have broken down long ago. The question may be raised as to what was accomplished by the specific treatment after all. It certainly has not given her any new heart muscle or restored the damaged valve, but may we not believe that it has at least partially checked the inroad of the disease into hitherto undamaged muscle? The neoarsphenamine has certainly accomplished at least one thing

each time and that is elimination of the pain, which tended to recur for a long time. This is not an uncommon experience in such cases.

Pure syphilitic myocarditis late in the disease is not an uncommon occurrence. Its three common manifestations are myocardial insufficiency, angina pectoris and heart-block. Myocardial insufficiency with aortic regurgitation has just been described. All the signs of failing heart are sometimes seen as a result of uncomplicated syphilis of the heart muscle. This condition responds much more readily to treatment than is the case with associated valvular defect. The conditions may be identical so far as the muscle is concerned, but a heart with a leaky valve requires better than normal muscle to compensate for the leak, while the heart not so handicapped has some margin of safety. The treatment therefore, may be bolder and better results may be expected.

An example of this type is found in Mr. G., an active man, aged fifty-five years, whose previous history is unimportant, and who denied venereal disease. He had complained of headache and bloody discharge from the nose for six months. He had also suffered some indigestion. Six weeks before he had begun to get short of breath and his legs had swelled for a few days. Examination showed a man with a lump on his forehead, an obstructed nose with a bloody discharge, double pleural effusion, ascites, and edema of the legs. His heart was much dilated (2.5 x 15 cm.) but showed no evidence of valvular disease. His blood-pressure was 130/78 and his urine contained a trace of albumin, the specific gravity being 1026 (kidney of passive congestion). The Wassermann was 4+. He was put on a dry diet, digitalis and potassium iodid with appropriate local treatment for the nose, advised by a rhinologist. The pleural effusions and dependent edema cleared up promptly but the ascites tended to persist. After a week he was given 1 mercury injection and about a week later 0.3 gm. of arsphenamine. Thereafter he was given a full course of the latter, followed by mercury inunctions and large doses of potassium iodid. In six weeks he was back at work. That was six years ago and he is still actively at work.

Angina pectoris due to syphilitic involvement of the coronaries or aorta is said to be not uncommon. I do not happen to have seen the former but have encountered the latter a number of times. The pain, anginoid or simple substernal distress, that so often accompanies aortitis, responds very satisfactorily to arsephenamine treatment.

Heart-block has been described a number of times as the result of a gumma or syphilitic degeneration of the bundle of His. The pathologists rank it as a cause of block more often than the clinicians, because it is readily found at autopsy and strikingly enough to be reported. Clinically, syphilis is comparatively rare as a cause of block. When it is found the block is seldom broken by anti-syphilitic treatment; but the treatment should be given to

check further involvement if possible, even though the offending lesion proves intractable to treatment.

Turning to the aorta, it will be recalled that syphilis invades this vessel early and often. During the secondary stage the treponemata tend to localize in the lymph spaces about the vasa vasorum. Here they may start a process so acute as to give rise to symptoms immediately, or as is more commonly the case, the process is so insidious that months or years pass before it makes itself manifest. In fact, it may remain latent throughout life, and never give any symptoms. It is supposed that latent syphilitic aortitis may account for the persisting Wassermann reaction which so often outlasts all symptoms. This seems reasonable when it is recalled with what confidence one turns to the aorta at autopsy in the case of a known syphilitic for the characteristic specific changes.

The symptoms of aortitis vary somewhat with the acuteness of the process. The most characteristic is *pain*, felt usually beneath the sternum, aggravated by anything that tends to raise the blood-pressure. The pain sometimes assumes the characteristics of a true angina. In the acuter forms there may be a little fever and some loss of weight, the patient being evidently ill. In the more chronic forms this side of the picture is lacking. There may be dyspnea, both on exertion or paroxysmal in character, which has been shown by Longcope to be of the reflex origin, depending upon irritation of the intima of the aorta. With these symptoms one finds evidence of valvular disease lacking, but there is a peculiar ringing accentuation of the aortic second sound, with possibly a systolic murmur over the aortic cartilage, transmitted into the neck. The area of aortic dulness is usually demonstrably widened and roentgen-ray plate shows quite early some dilatation and possibly increased density in the aorta. In this type of case, brilliant results are obtained by specific treatment, and one may have the satisfaction of feeling that the development of aneurysm has been prevented. The treatment, as always in cardiac vascular syphilis, should be begun cautiously, but in the absence of untoward reactions, it may be increased soon to maximum doses, and should be continued with all the throughness that syphilis always demands.

Aortitis with aneurysm superadded is a much more serious situation. When a weakened spot in the main arterial trunk gives way and starts to bulge, something has started that leads to certain destruction unless it is somehow checked. The pathologist long since showed us how Nature sometimes succeeds in checking the development of an aneurysm through the deposition of layer after layer of clot within the sac, the clots becoming more or less organized and reinforcing the weakened aneurysmal wall. This is the process which must be borne in mind, whatever else is done about the situation—and much else may be done. And so, when you encounter the syphilitic patient with a brassy cough, the husky

voice, the substernal pain, with a pulsating mass in his chest and perhaps signs of pressure on this neighboring organ or that, two lines of treatment present themselves to you: one the endeavor to bring about clotting within the sac, and the other, direct attack upon the syphilitic process. The former is best accomplished by means of the old Tufnell treatment or some modification of it. This consists of strict rest in bed with limitation of both fluids and food. In large saccular aneurysms, perhaps wiring and electrolysis should be tried as advocated by Hare. I believe specific medication should always accompany this treatment, and should be carried out in about the same manner as that outlined in the case of aortic regurgitation with broken compensation.

Through the courtesy of Dr. D. W. Waugh, I should like to report the case of a man whom I first saw while associated with him thirteen years ago. Mr. B. was at that time forty-four years of age. He had had smallpox and yellow fever but denied venereal disease. For a year he had had substernal pain radiating down both arms, and made worse by exertion. It had been growing gradually worse and had become so severe that he got but little sleep at night. He could not lie on either side. He had a cough and was hoarse. Examination showed a slight pulsating fulness in the left interspace, over which could be felt a thrill, and a soft murmur was heard which was audible in the back as well. Dr. Arrowsmith reported paresis of the left vocal cord, and fluoroscopy revealed the presence of an expansile tumor in the mediastinum, corroborated later by a plate. His Wassermann reaction was positive. He was kept in bed on a limited diet for seven weeks, during which time mercury and iodide were given by mouth. The pain practically disappeared in about two weeks though he had periods of some return of the pain for several months. After three months he returned to work and got along very well for about five years. At this time he developed violent pain in the back, radiating around both sides of the chest. At this time his Wassermann reaction was 4+, his spinal fluid being negative. Another roentgen-ray showed practically no change in the condition. He was kept in bed for three weeks and was given one dose of arsphenamine, but he refused to take any more and was therefore again placed on mercury by mouth and large doses of iodide. The pain promptly cleared up, and in the seven years which have elapsed since that time, he has only had occasional periods of mild pain which are quickly controlled by mixed treatment.

Syphilitic disease of the cerebral vessels usually comes to our notice in the form of thrombosis, involving most commonly the middle cerebral artery or some of its branches. It results most typically in hemiplegia, with or without aphasia, coming on rather gradually. If there is complete occlusion, the hemiplegia will be permanent, but partial occlusion may result in more or less transient

or incomplete palsies. In any event treatment is most unsatisfactory.

Conclusion. The fact should be emphasized that a great gain has been made in the recognition of the syphilitic nature of many cases of aortic insufficiency, aneurysm and myocarditis, and that appropriate treatment of these cases from this point of view, offers them a far better chance of comfort and prolongation of life.

RHEUMATOID ARTHRITIS WITH REMARKS ON THE USE OF COLEY'S TOXIN IN THE TREATMENT OF THIS CONDITION.

By Robert Torrey, M.D.,

and

Thomas Klein, M.D.,

philadelphia.

(From the Medical Department of the Philadelphia General Hospital.)

There are many classifications of the chronic diseases of the joints and much confusion exists in the nomenclature of these conditions. Reports of series of cases of arthritis, chronic rheumatism, rheumatic gout and allied conditions leave us in doubt as to what condition or disease has been under discussion. Particularly deplorable is the confusion which exists in the consideration of rheumatic fever as an acute arthritis which may go on to a chronic arthritis, eventually becoming arthritis deformans or chronic rheumatism. This view is a common one, much more common than most of us realize, and is unfortunate because through it the danger of rheumatic fever which is entirely a question of cardiac damage is overlooked, while attention is focussed on the joint. Also the serious aspect of an early rheumatoid arthritis may be ignored if the case is considered as one of mild acute rheumatism or rheumatic fever.

As McCrae[1] has stated, it is difficult to make an absolute separation of cases of chronic deforming arthritis into hypertrophic and atrophic forms, as there may be an overlapping of both these tendencies in a given case; but it will be found that most cases of generalized or multiple chronic arthritis show a definite tendency toward certain general characteristics which serve to place them in one or the other of these classes. No purpose can be served by an endeavor to augment the existing classifications which are already too numerous and too complicated, but a simple tabulation of the most frequent descriptive or classifying terminology may simplify the picture of these conditions.

Rheumatic Fever. This disease does not tend to become chronic; exceptionally where infection is persistent in the pericardium, fre-

quently repeated exacerbations recur with a simulation of chronic arthritis. Also where secondary streptococcic infection of the valves is present with bacteriemia, recurrent joint infection may take place. In either of these conditions the cardiac picture will properly place the disease. Otherwise rheumatic fever has nothing in common with chronic arthritis. The cardiac effects of rheumatic fever are of profound importance; the importance of the arthritis is negligible. When recovery takes place recovery is complete. There is little or no permanent atrophy and no bony change, contractures and fibrosis are not serious, and the joint is functionally as good as ever.

This condition must be sharply separated from chronic arthritis and is discussed in this connection, only for the purpose of emphasizing this distinction.

I. Chronic Arthritis. Arthritis Deformans.

Chronic Arthritis Primary Progressive Polyarthritis Chronic Non-suppurative Arthritis Chronic Infectious Arthritis Arthritis Deformans	Arthritis Deformans	Atrophic (Rheumatoid Arthritis) Hypertrophic (Osteoarthritis)

These terms are used by different authorities more or less loosely in describing the same conditions. By "infectious arthritis" demonstrable infection of the joint cannot be inferred and this meaning is not intended. If a focus of infection can be demonstrated, which is a probable causative factor in the arthritis, then this term may be used. Chronic non-suppurative arthritis is a descriptive term which commits to nothing. Arthritis deformans, in its common usage is more definite and more descriptive. It is also used by the surgeons, however, to describe the end-results of any single joint inflammation, including even old healed tuberculous lesions of the hip-joint; but in its ordinary medical usage refers to multiple chronic arthritis. As commonly applied these terms may be considered as practically synonymous, inasmuch as the same individual might be classed by different authorities in any one of these groups.

These groups taken together may be divided broadly into an atrophic and a hypertrophic class. Sometimes it is difficult thus to place a case but in general this can usually be done.

Atrophic Form. By atrophy is meant not only atrophy of the bone but also atrophy of all the joint and periarticular structures, atrophy of the skin, and particularly atrophy of certain muscle groups anatomically related to the joint concerned. This condition is *rheumatoid arthritis* and is fairly clear cut in its characteristics.

Starting with acute inflammation of joints, atrophy of the muscles appears with great rapidity. It may even appear before the joint inflammation. The distribution of these lesions is symmetrical. The course is progressive and chronic, interrupted by acute exacer-

bations, also symmetrical. In the early stages inflammation and atrophy are the distinguishing features. In the late stages atrophy and contracture. Ankylosis which may be extreme, is not caused by bony change but by atrophy, contracture, fibrosis and dislocation.

Hypertrophic Form (Osteoarthritis). In this class is included those cases in which bony overgrowth is the distinguishing feature. Ankylosis is the cause of disability. Atrophy is not a marked feature. There may be atrophy from disuse, but this bears no resemblance to the atrophy of the above class. The skin is usually well nourished and subcutaneous fat remains. In place of the emaciation characteristic of the former class many victims of this condition become obese and show little muscle-wasting after years of immobility.

Contrast this condition with the almost total wastage of certain muscle groups seen in the course of a few weeks in rheumatoid arthritis.

II. **Septic Joint.** By septic joint is meant that condition where the infecting organism is present in the joint and by its direct action on the joint tissues causes the damage. The gonorrheal joint is the commonest example of this. It must not be forgotten that chronic prostatitis or vesiculitis originating in a gonorrheal infection may become a focus of infection for a generalized arthritis of the first class or that a single chronic septic joint may itself be the focus activating a more or less generalized arthritis of a different nature.

III. **Trophic Joints.** In considering trophic joints, there are certain cases of arthritis where it seems possible to attribute the trouble wholly to trophic disturbance resulting from a recognized lesion of the nervous system and safely to disregard other factors, as in the Charcot joint of tabes or in certain cases of atrophic arthritis occurring in connection with syringomyelia, and possibly in the arthritis which is so frequently seen in connection with Parkinson's disease. Probably many cases of spondylitis are purely trophic in origin.

We shall later take up briefly the profound importance of trophic influences in the development of rheumatoid arthritis (the atrophic form of arthritis deformans). The central nervous lesion, though it certainly exists, is here not demonstrable, and other factors, as focal infection, cannot be disregarded.

IV. **Metabolic Joints.** Gout is the chief condition concerned in this class of arthritis. It is impossible to disregard the effect of metabolic variations on chronic arthritis in general, as has been well demonstrated by the exhaustive work of Pemberton.[2] But in gout we appear to have a condition where the products of infection do not play a part in the production of the joint condition and where the toxins concerned are purely the products or results of perverted general metabolic processes or local metabolic failures.

These cases certainly can, in many instances at least, be clearly set outside of the first class.

V. Spondylitis. Spondylitis which often exists without involvement of joints elsewhere, is also frequently seen in connection with generalized arthritis. In rheumatoid or atrophic arthritis, the spondylitis may be hypertrophic in type. Hypertrophic changes may occasionally also be seen in the articulations of the hip and the jaw in cases where the arthritis elsewhere is atrophic; in other words, these articulations situated near the axis of the body may behave differently from the joints more distantly placed.

Chronic villous arthritis is frequently set down as a separate class among the arthritides. This condition may occur in an isolated joint; it is frequently or usually symmetrical in its distribution; muscle atrophy is not marked as in rheumatoid arthritis; atrophy of the cartilages does not occur. There is great swelling and deformity of the joint cavity due to villous overgrowth, ankylosis takes place secondarily with decrease of deformity and the condition becomes an osteoarthritis. This possibly should be classed as an early form of the hypertrophic form. Also, of course, villous overgrowth may take place in isolated joints as a result of trauma or from other causes not related to generalized arthritis.

Syphilitic generalized arthritis is certainly a rarity if it exists at all. It must be borne in mind that in the presence of syphilis, tissue repair is not normal and an acute infectious or inflammatory process which would otherwise promptly clear up may persist simulating a chronic condition. The observed fact that such a condition clears up promptly under anti-luetic treatment does not mean that this condition was syphilitic any more than the commonly seen clearing up of an unresolved pneumonia under mercury and iodid means that the pneumonia was syphilis of the lung. These conditions are often thus interpreted and thus reported.

Fibrositis may simulate arthritis. While joint function is hampered by surrounding fibrous change, this condition is not primarily of the joints. It is probably due to an infection and is possibly related to or identical with rheumatic fever. It seems to occur more frequently and in more aggravated form in Great Britain than in this country—just as rheumatic fever is certainly more widely prevalent and more severe in its fibroid changes in England than it is with us.

Panniculitis. This condition, well described by Stockman,[3] does not concern the joints. It may superficially resemble the swelling of a villous arthritis, and this swelling being at times definitely tender, may give rise to pain on motion of the adjacent joint.

The distribution of the lesions in generalized arthritis, and particularly in the atrophic form, rheumatoid arthritis, is so perfectly symmetrical that the control of the distribution most probably in these cases lies in the central nervous system. Symmetry is most

exact not only in the onset of acute inflammation but in the development of contracture. If a joint in a finger is fixed in flexion, the corresponding joint on the other hand is flexed; if another joint is overextended, the corresponding joint of the other hand will be found in overextension; and this symmetry persists not only in type of deformity but in degree.

Where rheumatoid arthritis is not symmetrical, we must look for a nervous cause for the lack of symmetry. In a case seen by one of us the patient had suffered a shell wound of the skull with brain injury and hemiplegia. Following an empyema of the chest, arthritis developed, involving both extremities on the paralyzed side. This arthritis resembled a rheumatoid arthritis in mode of onset. It cleared up after free drainage of the chest. Subsequent attacks were limited to the same side until, with a very severe attack, the hitherto sound side was affected in a perfectly symmetrical distribution but in a milder degree.

Arthritis of either the atrophic or hypertrophic types will be found to be present in a much more severe degree on the paralyzed side in hemiplegias. We recently observed 3 instances of this phenomenon in a single ward at the Philadelphia General Hospital.

With a tendency to generalized arthritis, severe arthritis may develop distal to an injury in a peripheral nerve.

Infection is certainly concerned in many if not most of these cases. It has been satisfactorily demonstrated in so many that its presence as a causative factor may be assumed in a certain number of the other cases. How does this infection operate to produce the joint lesions? In what way can it work to produce the absolute symmetry observed throughout all stages of the disease? The central nervous system must determine the distribution. It is not conceivable that infection of the joints themselves could produce the symmetrical result here seen except under nervous control.

Many nervous conditions, resulting in profound physiological or structural alteration, show little histological change in the cells in which the trouble originates. Adequate and comprehensive microscopical studies of the brain and cord in cases of rheumatoid arthritis are apparently lacking, but the seat of trouble seems to be in the cord. In the hypertrophic form no such definite statement can be made. The sympathetic system seems to play a part in some cases at least, but its importance is probably slight as compared with that of the cord.

It seems probable that the assumed cord lesion is the result of toxic action and not an infection of the cord itself. The latter ought to give a very definite histological picture with which we almost certainly would be familiar.

Treatment. The treatment of chronic arthritis is a subject which has been approached from many angles and unfortunately many reports and discussions are misleading because of a lack of clear

understanding as to the type of disease under discussion. We are confining our discussion to the treatment of rheumatoid arthritis, which we consider to comprise a definite group of cases, showing certain distinguishing characteristics and tendencies. The arthritis of rheumatic fever, as has been said and reiterated, tends to recovery without joint damage. Many cases of arthritis reported as cured by various methods of treatment belong to this class. Metabolic or gouty arthritis demands appropriate treatment and yields well to treatment if joint destruction is not advanced. Chronic villous arthritis is said to respond well to surgical measures, the joints being opened and the hypertrophied synovial villi being resected with benefit (Swett[4]). Septic joints are surgical, though a chronic septic joint may be a focus of infection, causing a generalized arthritis.

Very striking results have been obtained in the treatment of arthritis by foreign protein injected intravenously or by so-called allergic reactions produced by other means. By such methods the acutely inflammatory reaction of rheumatoid arthritis can be promptly reduced or inhibited. Interest in these methods was stimulated by the papers of Miller and Lusk in 1916[5] and the simultaneous and subsequent publications of Jobling, Peterson,[6] [7] and others. At that time we were treating a number of cases of rheumatic fever and chronic arthritis by intravenous methods in the wards of the Philadelphia General Hospital. We felt that the treatment of rheumatic fever by such drastic methods was unjustifiable as far as it applied to the arthritis, but endeavored to ascertain whether the tendency to the development of carditis in rheumatic fever could be favorably influenced by such treatment.[8] The importance of arthritis in rheumatic fever is negligible, and the main concern in treatment must be regarding the cardiac condition; but the many papers published at that time gave no hint that this essential phase of the situation was being seriously considered. Attention was focussed on the joint in rheumatic fever, and cases of rheumatic fever and rheumatoid arthritis were not differentiated. We were unable to formulate conclusions regarding the influence of intravenous therapy in the prevention of cardiac complications in rheumatic fever. It can be clearly stated, however, that by intravenous therapy (the so-called allergic reaction or protein shock therapy) the acute inflammatory arthritis of rheumatic fever or the acutely inflammatory phase of rheumatoid arthritis can be checked, inhibited or temporarily put in abeyance.

Intravenous injections are not satisfactory, in that the dosage necessary to produce a given reaction cannot be gauged. A small dose may give a very heavy reaction. Reactions are severe and sometimes alarming. This method is not well adapted to the frequent repetition of doses necessary in chronic arthritis.

In looking for a substitute for intravenous medication we chose Coley's toxin, prepared from cultures of a virulent streptococcus

originally derived from cases of erysipelas combined with *B. prodigiosus*. This preparation had been used for many years in the treatment of sarcoma and experience showed that it was constant in its action and toxicity; the preparation was relatively stable and, injected intramuscularly, it could cause a reaction very similar to the reaction obtained by intravenous injection, but the degree of reaction could be controlled by varying the dose. Experience in treating sarcoma had shown that repeated injections could be given satisfactorily over long periods of time.

We have used Coley's toxin in the treatment of the inflammatory phase of rheumatoid arthritis and have found it satisfactory. Starting the dose at one-quarter of a minim, it is increased by doubling the dose until a reaction occurs. The doses are given at intervals of two to five days at first, preferably about five days. At a five-day interval a given reaction can usually be approximately duplicated by an increase of 50 to 75 per cent over the previous dose.

Focal reaction in the joint with increased soreness may occur after the first two or three injections. This rapidly disappears and a period of amelioration may be expected lasting at first for a day or two and increasing in length after each injection. The interval between injections may be increased to from seven to ten days. As the dose of toxin is increased to about seven or eight minims, a point is reached where little further tolerance is secured and reaction to this dose seems about constant. Local reaction is marked as the dose increases, but focal reactions in the joint cease.

In our experience this method of treatment has been successful in combating the acute inflammatory reaction in the joint. This, of course, is only one phase in the treatment. Contractures, which are responsible for most of the permanent deformity in rheumatoid arthritis, can be overcome surprisingly well by persistent effort. The adaptation of some means of extension by weights is the best means in most cases. In treating contractures which flex the knees, a modified Buck's extension which the patient can attach or release, and having the patient exercise the muscles against this extension, is most satisfactory. A similar apparatus can be hooked to the wrist to extend to the elbow. Baking is useful where fibrosis is a factor and manipulation and massage by a skilled and careful operator are of great service.

It is superfluous to say that the first requisite of treatment is the eradication so far as possible of areas of chronic infection. The most frequently implicated regions seem to be the alveolar process; the next in frequency the tonsil; the prostate and seminal vesicles are certainly responsible for many cases of generalized arthritis. Infection of the accessory sinuses account for a number of cases and infection of the intestinal tract for some. Following the influenza epidemic, intrathoracic infections, such as imperfectly drained empyema of the chest, were frequent causes. Pelvic infec-

tion in the female is probably seldom a cause of arthritis. No dead teeth should be permitted to remain in an arthritic patient; no tonsils should remain if they are suspicious. The clearing up of obvious areas of infection may be sufficient treatment in some cases, but unfortunately is usually not enough, and we never know whether the real source of infection has been attacked.

In treating a case of rheumatoid arthritis, we must have in mind the pathological features causing disability in this condition, atrophy and contracture and fibrosis, and combat these by appropriate measures. Also we must realize that continued inflammation in the joint seems frequently to cause atrophy and contracture. It is not necessary to postulate any specific action on the supposed infection by vaccines, bacterial toxin or intravenously administered substances. The allergic reaction may in itself be accompanied by a general detoxicating effect, and the injection of bacterial toxins may increase the tissue resistance to toxins of this type, so that the joint tissues no longer respond to irritation by an inflammatory reaction.

It is important to recognize rheumatoid arthritis in its early stages and to institute treatment before atrophy and contractures are advanced. This can be done if the characteristics of the disease are appreciated, particularly the symmetrical distribution of inflammation and atrophy.

Conclusions. 1. Rheumatoid arthritis should be clearly distinguished from rheumatic fever before atrophy and contractures have reached advanced stages.

2. Focal infections should be promptly attacked, and mechanical measures employed to overcome contractures. The inflammatory reaction in the joints can be overcome by increasing doses of Coley's toxin administered intramuscularly. The reaction to injections of Coley's toxin resembles the reaction to foreign protein injected intravenously but the dangers and difficulties attendant on intravenous therapy are avoided.

3. In our experience with this method of treatment, extending over several years, the use of Coley's toxin intramuscularly has been successful. We consider it the most important of the various measures employed in treating rheumatoid arthritis.

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REVIEWS.

THE TREATMENT OF DIABETES MELLITUS. By ELLIOTT P. JOSLIN, M.D., Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital; Physician to New England Deaconess Hospital. Third edition. Pp. 784; 30 illustrations. Philadelphia: Lea & Febiger, 1923.

THE name of diabetes is almost synonymous with the name of Joslin. When one thinks of the treatment of this condition and the part played in it by Americans one always thinks of Dr. Joslin. The universal recognition of his ability in the handling and management and treatment of this disease naturally may be considered a satisfactory index of his ability to put into writing what he knows about this disease. The splendid results the first two editions of this book met with are also indicative of the successful reception the book received from the medical profession. Now this present edition, the third, is of particular value and interest because of the discovery of insulin and because of what Dr. Joslin has to say about it. Joslin was one of the first to use the preparation, and certainly is one of the pioneers in the spreading of the clinical knowledge of this preparation, and to him credit is due for many improvements in the management of the patient with this disease. Presumably on account of the importance of this epoch-making discovery of Banting the newest section of the book on insulin is placed first, a hundred pages being devoted to this subject. After this follows the older sections of the book somewhat the same as they appeared previously. There is little that can be criticised in the work of Joslin. He has added much new matter and the material on insulin is up-to-date almost to the last minute before going to press; in that way he has included in the work, one might say, almost the very latest of the experimental and clinical work on insulin. It is interesting to note some of Joslin's methods in the treatment of this disease. He has a tendency to give considerably more protein than is usually given. He has also comparatively little fear of fats, and like most of the workers on diabetes at the present time, he has a tendency to omit the use of alkalies in the treatment of coma. Lastly, and what to the reviewer seems most important, he aims to keep the urine continuously sugar-free, a procedure which varies somewhat in the different diabetic clinics throughout the country.

Some have the patient use insulin only to the point where traces of sugar are found in the first morning specimen of urine. Altogether the book is really a wonderful monograph. The author has succeeded most admirably in getting over to the reader much of the enthusiasm which he has been able to instil in his spoken words.

M.

APPLIED ANATOMY AND KINESIOLOGY. By WILBUR PARDON BOWEN, M.S.; edited by R. TAIT MCKENZIE, B.A., M.D., M.P.E. Third edition. Pp. 352; 217 illustrations. Philadelphia and New York: Lea & Febiger, 1923.

THE understanding of accurate muscular action is most vague even in the minds of otherwise well-trained physicians. A great stimulus to furthering this important knowledge was added by the results of the war. Thousands of cripples and disabled ex-soldiers have been made useful members of society by a reëducation of muscle action. The knowledge of muscle action is just as important to a physician as is the knowledge of nerve function or any other bodily function. This book should help in placing physical education upon the plane that its importance demands and will well continue more and more to demand of the medical advisor. Both the authors are admirably fitted for the intelligent presentation of their subject by virtue of these long experiences in the physical training of hundreds of school and college students.

E.

INDIVIDUAL GYMNASTICS. By LILLIAN CURTIS DREW, Director of Department of Corrective Gymnastics, Central Branch Y. W. C. A., New York. Second edition. Pp. 206; 109 illustrations. Philadelphia and New York: Lea & Febiger, 1923.

PROPERLY applied corrective exercises are exceedingly important in modern life. Such a work is especially welcome in these days of preventive medicine. The value of corrective physical exercise in the developmental periods of years and even in the ordinary individual is a great one. This book not only does this, but indicates the proper relation which gymnastics and other forms of exercise bear to the practice of medicine. The student in this departmental work can be guided intelligently and safely by this little book whose author has had a world of experience in handling individuals as well as groups. It is a book for students of medicine, school teachers, physical instructors and the average individual.

E.

THE FUNDAMENTALS OF BACTERIOLOGY. By CHARLES BRADFIELD MORREY, B.A., M.D., Professor of Bacteriology, Ohio State University. Third edition. Pp. 344; 171 illustrations, 6 plates. Philadelphia and New York: Lea & Febiger, 1923.

ATTENTION is called to a review of the previous edition of this book (AMER. JOUR. MED. SCI., 1921, **162**, 750). In this edition several additions and revisions have been made. Most conspicuous of these changes is the substitution of the system recently adopted by the Society of American Bacteriologists for Migula's classification of organisms. This we consider a step in the right direction, although as given here the new classification is not as complete as might be desired. In addition, revisions concerning the standardization of material to a definite H-ion concentration have been included. J.

ARBOREAL LIFE AND THE EVOLUTION OF THE HUMAN EYE. By E. TREACHER COLLINS, F.R.C.S., Consulting Surgeon to the Royal Ophthalmic Hospital, London. Pp. 108; 25 illustrations, with colored frontispiece. Philadelphia: Lea & Febiger, 1922.

THIS is an extension of the Bowman Lecture, given before the Ophthalmological Society in 1921. By means of comparative anatomy and comparative histology the author succeeds in delineating the structure of the human eye in a most interesting way. He adopts an evolutionary point of view and shows how the human eye has become adapted to its present uses. For comparison he describes the structure of the eyes of a number of other species, and points out their various adaptations. Thus we have panoramic, binocular and stereoscopic types of vision. In each of these types the parts of the eyes show definite structural variations, which can be readily recognized, some with and some without the microscope. Thus the relative size of the cornea and the size and shape of the pupil, as well as the size and shape of the lens, vary greatly and the variations are readily seen. The differences in the ciliary body and in the retina require study with the microscope to be determined. The book will appeal to all interested in the eye and vision, clinicians zoölogists and psychologists as well. A.

THE PHYSIOLOGY OF TWINNING. By H. H. NEWMAN, Professor of Zoölogy, University of Chicago. Pp. 230; 71 illustrations. Chicago: The University of Chicago Press, 1923.

THE author's previous book on this subject, *The Biology of Twins*, published six years ago, was largely morphological in char-

acter and dealt with mammals only. In the present volume the scope is extended to include the theories relating to the causes of twins and to the influences of twins upon each other, as well as to describe all the known types of complete or partial one-egg twinning in the animal kingdom. Separate chapters are devoted to twinning in starfishes, earthworms, fishes, birds, armadillos and other vertebrates. Of the several chapters describing human twinning, perhaps the most interesting is the one on the developmental hazards of human twins. As to the interpretation of double monsters, the author believes that they are the products of incompletely divided single embryos and not the fusion of two embryonic axes. The book is an important contribution to this special field. A.

PROTISTS AND DISEASE. By J. JACKSON CLARKE, F.R.S.C., Senior Surgeon to the Hampstead and Northwest London Hospital. Pp. 229; 61 illustrations. New York: William Wood & Co., 1923.

THE search for the causal organisms of disease leads the student into many regions of biology. The author of this work, at once a surgeon and a pathologist by vocation, has paid attention for many years to the protists, or group comprising the lowest animals and plants. In this, his sixth volume on the subject, he discusses a number of these organisms and their relation to some of the more serious diseases of the human body. A.

RHUS DERMATITIS. By JAMES B. MCNAIR, M.D. Pp. 300; 15 illustrations and 3 plates. Chicago: University of Chicago Press, 1923.

MCNAIR's monograph is of the welcome sort in which the research has been deliberately planned, recorded in detail and supplemented by an analysis of the literature. He begins with the bionomics of the several poison ivy species, and thereafter covers the anatomy, modes of transmission of the toxic resin (not fat) from plant to person, the chemistry of the poisonous principle and finally the pathology, including immunity, differential diagnosis and treatment of the disease. Most of these sections have appeared in the literature from time to time, but while the book is thus largely a collection of reprints the work was so planned that there is a perfectly satisfactory thread of continuity between the sections as they now appear in book form.

Some of the points which will command the attention of the medical man are as follows: The active toxic agent is a non-volatile resin which McNair calls lobinol. Its formula is unknown, but it is a probable phenol. There have been a few cases of fatal internal ivy poisoning. Chewing of leaves (to induce immunity) has produced perianal dermatitis, internal poisoning and one death. In 49 bed-fast cases, 35 per cent showed albuminuria, and one patient developed acute nephritis. Leukocyte counts ranged from 14,000 to 31,600. There was no eosinophilia. Immunity is only relative, apply sufficient poison and the so-called immunes will react. Ferric chloride in aqueous 5 per cent solution is recommended as the rational antidote.

Thirty-five pages of abstracts and a bibliography of sixty-seven pages make this book a mine of information.

Viewing McNair's book on the whole, the reviewer is impressed in the wise that although the subject of rhus dermatitis has thus come to appear exhaustively in book-form it must not be presumed that it itself has been exhausted, and that we can relax in our inquiries into the subject. This must be avoided. Rather has McNair established a fine nucleus around which new findings ought to accumulate, and these are still sorely needed in respect to the pathology and treatment of the disease. W.

A TEXT-BOOK OF CHEMISTRY FOR NURSES. By FREDUS N. PETERS, A.M., PH.D., Professor of Organic Chemistry, Hahnemann Medical College, Kansas City. Second edition. Pp. 302; 39 illustrations. St. Louis: C. V. Mosby Company, 1923.

THIS manual deals with the subject in a simple rather than an elementary style. Wherever possible the practical aspects of chemistry and the relation of the bases, acids and salts to medicine have been discussed. Of value to the nurse will be the various tables, the chapter on common poisons and the compilations of scientific and common names and terms for chemicals in the appendix and glossary. W.

OBSTETRICS FOR NURSES. By CHARLES B. REED, M.D., Obstetrician to Wesley Memorial Hospital, Chicago. Second edition. Pp. 300; 144 illustrations, including two color plates. St. Louis: C. V. Mosby Company, 1923.

THAT Dr. Reed's book has necessitated a second edition would seem to reflect that his method of presentation of this subject had

been approved in a wide degree. The one criticism that might be offered to this book, which is not a manual on nursing in obstetrics, but, as its title says, obstetrics for nurses, is that it is too full, too advanced, too technical, as for instance when he offers to nurses the indications and contraindications for using pituitrin. For the most part the field of obstetrics is well covered, and much of the text has been revised. W.

Discours de la Nature de l'air; de la Vegetations des Plantes. By Edme Mariotte (1620 ca.–1684). Reprinted. Paris: Gauthier–Villars, 1923.

Not only does the present rapid growth of scientific discoveries tend to obscure the work of the pioneers in science, but also their chef-d'oeuvres are as a rule extremely expensive and scarce. For this reason, Gauthier–Villars are publishing a series of "Maitres de la Pensée Scientifique," under the editorship of Maurice Solovine, of which series the present volume is the sixteenth. Although all branches of science are represented, the cultured physician will find many interesting contacts in accurate editions of the most important works of Huygens, Lavoisier, Spallanzani, Ampère, La Place and Pascal at the ridiculously low price of three to four francs a volume. K.

The Action of Alcohol on Man. By Ernest H. Starling, Foulerton Professor of Physiology, University College, London. Pp. 291; 12 illustrations. London: Longmans, Greene & Co., 1923.

Dr. Starling, who has described the action of alcohol on man from a purely scientific physiological standpoint in the light of our most recent knowledge, comes to the conclusion that "in moderation it is difficult to appreciate any harmful effects from its use, whereas when temperance is abandoned and alcohol is used immoderately its effects are evil and fraught with disaster to the individual and damage to the community." The book also includes three separate essays, one on "Alcohol as a Medicine" by Dr. Robert Hutchinson; one by Sir Frederick W. Mott on "Alcohol and its Relation to Problems in Mental Disorders," and one by Dr. Raymond Pearl on "Alcohol and Mortality." Mott concludes that alcohol plays a relatively unimportant part in the production of certified insanity; and Pearl states that while the moderate consumption of alcoholic beverages does not sensibly shorten the mean duration of life nor increase the rate of mortality as compared

with that of total abstainers, still its excessive use definitely diminishes the mean duration of life and increases the rate of mortality. The evidence as well as the opinions of all these writers would seem to indicate that the abolition of all alcoholic drinks in so-called civilized society is a mistake and contrary to the permanent interest of the race. The book lays stress on all the benefits which the present generation may obtain by the use of alcohol. Though Stockard's experimental studies of the influence of alcohol on the given cells and his analysis of the hereditary transmission of degeneracy and deformity by the descendents of alcoholized mammals, are mentioned, the benefits that might accrue to the race in the future, as shown by Stockard, by the elimination of the weak, the unfit, and the defective, might have been further dilated upon as the most important argument for the repeal of the eighteenth amendment of our Constitution. O.

THE NEW DIETETICS. By JOHN HARVEY KELLOGG, M.D., LL.D., F.A.C.S., Superintendent of Battle Creek Sanitarium, President of Battle Creek College. Second edition. Pp. 1021; 18 illustrations. Battle Creek: The Modern Medicine Publishing Company, 1923.

THIS is an interesting and stimulating book which the reviewer recommends to physicians. It contains, however, too much unproven opinion presented as fact, and too many examples of "partisan inference" to make it a safe guide for "the trained nurse, the intelligent housewife, as well as the professional dietitian"—all of whom the author includes in his presentation. The author is a crusader against what he believes to be one of the greatest ills that civilized man is subject to—viz., colonic stasis and autointoxication from high protein diet and other "unbiological practices." F–H.

DIAGNOSTIC METHODS. By HERBERT THOMAS BROOKS, A.B., M.D., F.A.C.P., Professor of Clinical Medicine, College of Medical Evangelists. Fourth edition. Pp. 109, 52 illustrations. St. Louis: C. V. Mosby Company, 1923.

THIS manual represents an attempt to epitomize the usual diagnostic methods employed in the study of patients. The author's ideals of accuracy and completeness have naturally come in conflict with the limitations of allotted space. The author wisely advises that in addition some extensive work on Clinical Diagnosis be used as a reference book. F–H.

INFECTION, IMMUNITY AND BIOLOGIC THERAPY. By JOHN A. KOLMER, M.D., Professor of Pathology and Bacteriology in the Graduate School of Medicine, University of Pennsylvania, and Member of the Research Institute of Cutaneous Medicine, Philadelphia. Third edition. Pp. 1210; 202 illustrations. Philadelphia: W. B. Saunders Company, 1923.

ONE might say in going over the third edition of Kolmer's textbook on Infection, Immunity and Biologic Therapy that it is almost a new book. This is due to two factors: First, that a complete revision was necessary as the previous two editions, appearing as they did before the war, were out of date on account of the rapid advances in this branch of medicine, while the second factor is the result of the large amount of new material which the author has seen fit to add to the work. The book is divided into five parts. Part 1 deals with general immunological technic, the second part with principles of infection, the third with principles of immunity, the fourth with clinical allergy and biological therapy and the last with a series of experiments arranged for the student. Discussing seriatim the several parts it may be said that Part 1 is a general description of the methods employed in preparing and making sera as well as the principles of collecting body fluids. Part 2 is a discussion of the general principles of infection. Part 3, the longest section of the book and probably the most important to the student, contains a most broad and at the same time a detailed discussion of immunity and immunological technic. In this section, of course, the greatest value is to be placed on a very thorough, minute discussion of the Wassermann complement-fixation test, particularly from the standpoint of the modifications which the author has introduced into this procedure. Part 4 is the section which should be of most value to the practitioner of medicine, as it contains a full exposition of allergy and the treatment of the condition as well as chapters on the use of sera, non-specific protein therapy, vaccines, blood transfusion, and so on. The last part is a series of experiments designed entirely for the laboratory instruction of the student. The work is a most splendid, first-hand presentation of the subject. It is not a compilation in any sense, as are so many books, but represents for the most part the result of the personal studies of a most indefatigable worker. There is little to criticise about the work. One might take exception at times to the lack of standardization in nomenclature. For example, in the classification of allergy, the terms that are employed vary considerably with different authors and Kolmer has seen fit to still further confuse the subject by adding a classification of his own. Of course, the obvious excuse is that the subject is so new that it has not had time to be standardized. M.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

Intravascular Injection of Iodized Oil.—SICARD and FORESTIER (*Compt. rend. Soc. de biol.*, 1923, **88**, 1200), making use of the great opacity to roentgen-rays and the remarkable tolerance of the organism to iodized oil (lipiodol), have succeeded in studying in man and animals many cavities and spaces until now unexplored. The subarachnoid and epidural spaces, the broncho-pulmonary tree, abscess cavities, etc., have been successfully explored without harm or danger. Their most recent work has been concerned with injections of the oil into different vascular trunks of the dog, watching by means of the fluoroscope screen and serial roentgenographs its distribution and passage through capillary beds. "Injection of 5 cc of the lipiodol into the femoral vein of a 5-kg. dog caused no respiratory or cardiac embarrassment, provided two to three minutes were taken for the injection. One may see under the screen white oily drops issuing from the needle and carried by the blood current with progressive acceleration to the iliac vein and then to the heart. Arriving in the right cavity of the heart, the drops are pulverized by the ventricular contraction, which projects the droplets with great speed into the pulmonary artery. After penetrating very nearly uniformly into the two branches of this artery, the droplets are quickly arrested in the capillary network of the different parts of the lung. The total time of travel from the femoral vein to the pulmonary stoppage was about six to seven seconds." These droplets disappear from the capillaries in ten to twelve minutes. Injection of 8 cc of the oil into the portal vein showed a very sluggish movement of the blood current, two to three minutes being required for even the larger branches in the liver to be penetrated. After one and a half hours all the oil appears still to be in the hepatic capil-

lary network. When arteries such as the femoral or carotid receive the injection there is very rapid distribution of the oil, with its appearance in the venous return within two minutes. No circulatory or other disturbances are caused in the animal unless the injection be made too rapidly. This work opens an interesting field for the study of the permeability of different capillary beds to oils and of the topography of the vessels in the intact organism. Also abnormal states of the circulatory apparatus may be directly studied.

Sickle-cell Anemia.—J. G. HUCK (*Bull. Johns Hopkins Hosp.*, 1923, **34**, 335) reports observations upon sickle-cell anemia, based on a study of 14 cases. Hitherto, only 4 cases have been recorded, the first by J. B. Herrick in 1910. The cases studied by the author occurred in three generations of two families. As a result of his observations, he concludes that sickle-cell anemia is "a hereditary disease, transmitted by and occurring in both males and females with equal frequency, in which the red cells of the blood acquire a characteristic sickle or crescent shape *in vitro*. The disease is characterized by certain typical clinical symptoms, especially those of anemia and leg ulcer." The disease has been observed only in negroes. No infective etiological agent has been discovered. No postmortem findings have been reported. The blood shows an anemia, the red cells varying between 1,500,000 and 4,000,000, the hemoglobin between 30 per cent and 63 per cent. The color index is usually normal or high. There is a slight increase in the white count (10,000 to 20,000) with increase in the percentage of polymorphonuclear neutrophiles. A few myelocytes, chiefly neutrophilic, may be observed. Cells of the large mononuclear variety are seen at times, phagocytizing red cells. "The poikilocytosis consists mostly of crescent or sickle-shaped cells with an occasional oat-shaped cell." Basophilic granulation and polychromatophilia are observed. Nucleated reds (normoblasts, intermediates and megaloblasts) may be found, chiefly normoblasts. No Cabot rings or Howel bodies have been observed. "Fresh wet preparations of the blood, that have been sealed with petroleum jelly, reveal a most interesting phenomenon. Immediately on examination of the preparation one finds only a few of the erythrocytes having a crescent or sickle shape, but after from six to twenty-four hours, from 25 per cent to 100 per cent of the cells, according to the severity of the disease, acquire bizarre forms." The cells show a slight decrease in resistance to hypotonic salt solutions. Reticulated cells, as demonstrated by vital staining, are greatly increased, even to 35 per cent. The bilirubin content of the serum is high. In the severe forms of the disease, the prognosis is unfavorable on account of a susceptibility to acute intercurrent infections, especially pneumonia and tonsillitis. Treatment is symptomatic.

A Warning Against the Use of Arsphenamine in the Treatment of Syphilis in a Hemophiliac.—ROSENBLOOM (*Jour. Lab. and Clin. Med.*, 1923, **9**, 57) reports the case of a colored man who had been bleeding from a tooth socket for two weeks following extraction of the tooth. His hemoglobin was 40 per cent and red cells 2,300,000. There was a history of an initial lesion fifteen years previous and the Wassermann was ++++. After attempting to stop the hemorrhage by transfu-

sion and the injection of horse serum, 0.6 gm. arsphenamine was given. Within an hour after this injection all his gums began bleeding alarmingly. This loss of blood was partly checked by adrenalin compresses but in spite of three transfusions and the use of coagulose, horse serum, etc., the bleeding continued until his death two weeks later. From this experience, and on the basis of experimental findings pointing to an interference with normal clotting by arsphenamine, Rosenbloom feels that the use of this drug is contraindicated in hemophilia.

Spinal Subarachnoid Block.—AYER (*Arch. Neurol. and Psychiat.*, 1923, **10**, 420) describes a method which consists of manometrical study of fluid by double puncture and comparison of fluids at different loci. For the hydrodynamical studies, the points of puncture are above and below the obstruction. The protein content of the fluid from below the point of obstruction is increased. Most of the fluids from below the obstruction are colorless. Fifty-three cases of block studies, 41 complete. Block was caused by tumors, by vertebral disease and dislocation and by meningitis. Below point of obstruction, pressure of the spinal fluid is either not affected or only slightly affected by such maneuvres as jugular compression. Of 104 cases, in which no block, complete or partial, could be demonstrated, 3 proved later to have compression of the cord. Two of these, however, showed marked increase of protein below the tumors. It would seem that the demonstration of block and the increased protein content of the fluid from the lower needle are valuable indices as to the permeability of the spinal subarachnoid space.

The Size of the Heart in Pneumonia.—LEVY (*Arch. Int. Med.*, 1923, **32**, 359) made teleoroentgenograms of 21 cases of lobar pneumonia and 8 cases of bronchopneumonia. Three normal young men and 1 patient with fever, due to pulmonary tuberculosis, acted as controls. Care was taken to secure proper alignment, and a simple geometrical method was used to complete the outlines of the cardiac shadow. The area so delineated was measured with a plain meter. The controls showed very little change in transverse or long diameters or in surface area. A variation of 1 cm. or more in one of the diameters, or of 10 sq. cm. or more in area was regarded as significant. Of the 21 cases of lobar pneumonia, 13 showed an increase in the size of the heart. Eleven of the patients were given digitalis; 10 were not. Of the 11 patients, 8 (72.7 per cent) showed cardiac enlargement; of the 10, 50 per cent showed cardiac enlargement. Eight cases of bronchopneumonia were observed, 2 showing a change in the size of cardiac silhouette.

The Treatment of Syphilis with Bismuth.—MCCAFFERTY (*Arch. Dermat. and Syph.*, 1923, **8**, 469) reports the treatment of 25 cases of syphilis, in all stages, by bismuth. Potassium and sodium tartrobismuthate is used. Two cc, or 20 cg. of active bismuth, suspended in oil, is given intramuscularly every four days. Twelve to 16 such injections constitute a course. There is evidence to show that this agent is as effective as arsphenamine in treating primary and secondary manifestations, although its action may be slower. Bismuth would seem

to be very useful in treating "Wassermann-fast" individuals, as well as those having an idiosyncrasy towards arsenic. Nothing definite can be said about its action in neurosyphilis. Pigmentation of the gums and stomatitis may occur. Local pain at site of injection is said to be negligible. A good working bibliography is added to this article.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Further Observations on the Blood-pressure in Cases of Urinary Obstruction.—O'Connor (*Jour. Urol.*, 1923, **10**, 135) states that complete drainage of the bladder in patients suffering from urinary retention is attended by a marked fall of systolic blood-pressure during the first forty-eight hours. During this period the renal function is diminished as shown by the phenolsulphonephthalein test and the quantitative determination of urea in the blood. If, however, the retained urine is gradually evacuated, the decrease in pulse pressure will be less marked, and the renal function only slightly diminished. Before instituting permanent drainage all patients in the preuremic or dehydrated condition should be amply supplied with fluid. This can be quickly and safely accomplished by intravenous injection of glucose solution. If satisfactory drainage of the bladder is continued, the blood-pressure is gradually maintained at a definite non-fluctuating level. Patients prepared for operation by waiting until this fixed blood-pressure level has been established have shown a very insignificant postoperative decrease in blood-pressure, especially when glucose solution is given intravenously, both before and after operation. Obstruction in the course of the urinary tract must be considered in many instances as a cause *per se* of high systemic blood-pressure. This may be equally true even through the residual urine is small in amount. In papillary epitheliomata hematuria is usually present being intermittent in character. Pain is noted in half of the cases. Pyelography reveals deformity of the pelvic outline in almost every case. This type of growth is seldom seen in patients under forty years of age. Metastases in bladder and ureter are common.

Operations for Inguinal Hernia Under Local Anesthesia.—Bloodgood (*Am. Jour. Surg.*, 1923, **37**, 185) describes the full technic of local anesthesia with one-quarter of 1 per cent of novacaine. He likewise gives detailed account of his technic for inguinal hernia. The author states that both Bassini and Halstead laid great stress upon

the transplantation of the cord. Follow up studies showed that the transplantation of the cord was not an essential feature in the operation for inguinal hernia for the chief cause of recurrence was the weakness or obliteration of the conjoined tendon and this was not in the position of the transplanted cord. Other recurrences, a very small number, could be explained by the large size of the cord, and in this group the recurrence occurred alongside of the cord. In a small percentage of the cases, the recurrence could be more easily explained by faulty suture or extreme weakness of the tissues available for suture. Healing of the wound is not as perfect in the hands of surgeons, not deeply experienced in local anesthesia. But the breakdown of the wound is usually confined to the skin and fat, and seems to have no influence on the result.

Vasostomy for Seminal Vesiculitis.—KIDD (*Lancet*, 1923, **2**, 213) says that a seminal vesicle infected with gonococcus or B. coli or other germ can remain blocked and full of the infecting agent for many years. The victim may suffer from relapsing fever and rigors from relapsing urethral discharges, from arthritis or iritis, from impotence and sterility, and from neurasthenia. In some cases the neurasthenia is so severe as almost to amount to a psychosis. The author definitely states that all these troubles except the irites can be cured by vasostomy. He feels that this procedure, which he describes at length should be used in all cases of chronic relapsing gonorrhea (or B. coli or streptococcal vesiculitis) in which there is evidence of a thickened closed vesicle or vesicles and in which four or six months' consecutive and careful treatment by massage, urethroscopy and so forth has failed to produce a cure. Vasostomy is also indicated for cases of chronic arthritis, with chronic relapsing epididymitis that do not yield to such treatment. It should also be used for cases of relapsing attacks of fever, rigors, pyuria, epididymitis caused by the colon bacillus or other germs such as streptococci. In the final group, he states that it should be used for many cases of severe arthritis in the early stages. Belfield has reported 83 cases of posterior urethritis, with acute vesiculitis and arthritis, where immediate amelioration has been obtained by vasostomy.

Secondary Signs of Gall-bladder Pathology.—LEONARD (*Am. Jour. Roentgenol.*, 1923, **10**, 521) says that roentgen-ray evidences of gall-bladder pathology is divided into two classes—direct and indirect: In the first are put the demonstrable stones and visible gall-bladders. In the indirect class are put the demonstrable changes produced by gall-bladder disease. This latter class is by far the most important. in it are included the pressure deformities, chiefly by the duodenum; the changes caused by adhesions including fixation of adjacent organs by adhesions, and deformities in outline of adjacent organs from adhesions; the field of gastric reflex (typical gall-bladder spasm); lastly the ampulla of Vater, when made visible by barium has, in the author's experience, been associated with some type of past or present gall-bladder disease.

A Conservative Treatment of Carbuncles.—LEWIS (*Ann. Surg.*, 1923, **78**, 649) says that only 3 cases of carbuncles treated by roentgen-ray

were found in the literature. Sixteen unselected cases of carbuncles treated by roentgen-ray are here reported. Only 2 of these 16 cases required operative treatment. Diameters of induration increased more than 2 cm. after roentgen-ray treatment in only 2 cases, and in 1 of these it was probably due to a too narrow protecting of the field of the roentgen-ray in giving the treatment. Sloughing and suppuration, and the skin sinuses through which this took place were surprisingly slight in the small and moderate sized carbuncles. The very large carbuncles resolved into enormous, sharply demarcated abscesses, which drained satisfactorily through the sinuses formed by sloughing of the overlying skin. Pain was relieved following the roentgen-ray treatment in the majority of cases. The duration of small and moderate sized carbuncles seemed much shorter with roentgen-ray therapy than under operative treatment. The duration of the very large carbuncles seemed about the same with roentgen-ray or operative treatment. Cosmetic results were superior with roentgen-ray. Great preference for the roentgen-ray treatment was expressed by patients with experience in other forms of treatment. The method seems relatively safe. The comparative absence of traumatism as compared with operation seems a protective measure of importance.

The Surgical Management of Gall-bladder Disease.—FINKENHEIM (*Zentralb. f. Chir.*, 1923, **27**, 1050) classified operated gall-bladder cases as chronic cholecystitis, acute cholecystitis, chronic cholecystitis with acute exacerbation. The last group contained approximately 40 per cent of a *large series* of 670 cases. Sixteen cases showed perforation, half rupturing into the peritoneal cavity, and half were walled off by strong surrounding adhesions and inflammatory processes. A second group is given of 74 cases, in 57 of which were found at operation the marks of definite processes of inflammation, but with no stones. In 17 neither inflammatory processes nor stones were found. A third class contains the empyema group, 115 in all, 98 of which had stones and pus, while 17 exhibited pus without stones. A fourth grouping contained 11 cases of hydrops. The fifth set embraces all grades of inflammatory interference in the common duct. Stones were present in 100 of 136 cases. The sixth group comprised 10 cases of gall-bladder ileus; while the seventh place in the classification comprised 41 cases of carcinoma. Complications or associated diseases were present in 32 cases. In 22 instances cholelithiasis was primary, appendicitis, ulcer of duodenum, and other diseases being secondary. In 10 cases the associated pathology was primary, and the gall stones secondary. Secondary operation occurred in 37 cases. The author finds the solution of operative procedure simple: Cholecystectomy is the routine procedure for cases with pathology localized in the gall-bladder, while cholecystostomy is reserved for those cases unable to stand general anesthesia for a long period, with disease of heart and lungs. The routine procedure for operations on the common duct was choledochostomy—choledochotomy with suture was performed in 30 cases. For mortality, 16 deaths occurred from pulmonary causes, 18 from cardiac failures, 8 from clotting deficiencies in the blood, peritonitis with perforation 10 cases, peritonitis without perforation 11, collapse and inanition 24, septicemia 2, and cachexia 2.

THERAPEUTICS

UNDER THE CHARGE OF
SAMUEL W. LAMBERT, M.D.,
NEW YORK.

Medical Methods of Controlling Hemorrhage.—KAYSER (*Med. Klin.*, July, 1923) writes that many methods such as hypertonic salt solution, organ extracts, coagulen, serum, peptone, etc., have been employed as aids to control hemorrhage, but as yet no one remedy has proved infallible. In addition, the surgeon has often to resort to medical means in cases of postoperative hemorrhage. Nonnenbruch and Szyska have investigated euphyllin and ethylenediamin as a means to increase blood coagulation. Euphyllin, one of the purin bodies, contains about 80 per cent theophyllin and about 20 per cent ethylenediamin. Euphyllin is employed as a diuretic and heart stimulant. They found that it increased the coagulation of the blood when used subcutaneously, intramuscularly or intravenously, this reaction reaching its highest point in four to five hours after injection, and the effect lasting up to twenty hours. Other workers found that the active principle of euphyllin in this reaction is ethylenediamin. Investigations showed that the latter used alone gives like results. Nonnenbruch believes that this substance acts on the blood indirectly, causing a mobilization of the substance in the blood that brings about coagulation. The author of this article thought of trying something combined with ethylenediamin to enhance the reaction of coagulation of the blood. The effect and action of calcium in the blood is well known. He took ethylenediamin acetate and a calcium salt and obtained a compound, crystalline in character and soluble in water, which he calls hämosistan. Using rabbits he found that 1 cc of a 10 per cent solution given intravenously resulted in a marked increase in the coagulation of the blood, reducing the time on the average from fifteen to five minutes. The peak of the reaction is reached in an hour and the effect is manifest up to forty-eight hours. No symptoms are evidenced. Hämosistan is given intravenously as other methods of administration are painful. It has been used in man in various clinics in Berlin, with results that are better than in the animal experiments. Ten cc of a 2 per cent solution is the optimum dose. It has been employed in hemorrhages of all kinds and may be secured in ampules.

The Treatment of Vincent's Angina with Trypaflavin.—In 14 cases of Vincent's angina, BUSCHMANN (*Deutsch. med. Wchnschr.*, 1923, **19**, 617) used trypaflavin, painting the throat each day for three or four days and having the patients gargle with a solution of trypaflavin. He claims that they have cleared up in from three to seven days.

Studies of Turpentine.—KLINGMÜLLER (*Deutsch. med. Wchnschr.*, 1923, **21**, 669) advocates the use of turpentine in those cases in which nonspecific therapy is used for temperature reactions. He uses a special

preparation called olobintin, which is a preparation of turpentine in oil. This injection causes the formation of a sterile abscess which is open when indicated.

The Effect of Alkalis on Gastric Secretion and Motility as Measured by Fractional Gastric Analysis.—LOAKWOOD and CHAMBERLIN (*Arch. Int. Med.*, 1923, **32**, 74) report the effects on gastric function of the administration of a standard dose of four commonly used alkalis. The antacids were all given with the Ewald meal and comparison made with control curves in 26 cases. Neither sodium bicarbonate, calcium carbonate, magnesium oxide or bismuth subnitrate seemed to affect the evacuation time of the stomach. This does not support Cannon's conception of the acid control of the pylorus. The phenomenon of bile regurgitation was also unaffected. The average free and total acidity was lower after the administration of the alkali in all observations on calcium carbonate and magnesium oxide. In rather less than one-fourth of the sodium bicarbonate tests it was actually higher. The average acidity was unaffected by bismuth subnitrate. After sodium bicarbonate the acidity rose to a higher point than in controls in about one-half the cases; after calcium carbonate, in one-fourth and after magnesium oxide in one-fifth of the cases. After bismuth, the acidity attained a higher point in only 2 of the 7 cases. The results with the different alkalis are not strictly comparable since the neutralizing power of soda is only one-half that of calcium carbonate and one-fourth that of magnesium oxide. It is possible that with a dose of soda equal in strength to the dose of calcium or magnesium, the acid rebound would have been less in evidence. On the other hand, the liberation of carbon dioxide when soda is administered may have acted as a direct stimulant.

The Pathogenicity and Treatment of Flagellate Dysentery.—According to WHITTINGHAM (*Brit. Med. Jour.*, May, 1923, p. 1799) flagellate dysentery is a pathogenical condition which if allowed to persist will eventually undermine the health of the patient and cause neurasthenia, and he states that all cases of recurrent diarrhea or neurasthenia for which no cause can be found and in which flagellates have been detected in the stools should have a course of treatment. Certain cases are simply carriers, and these are a great source of danger as they may infect others. He says that flagellate dysentery may be cured in at least 50 per cent of the cases by the treatment he advocates. The patient is put to bed and kept upon as light a diet as possible for three days. At the same time sodium bicarbonate is given thrice daily in 15 grain doses, to clear away any mucus coating the internal surface of the gut. To further clear the intestines, 3 grains of calomel are given at bedtime on the third day, followed by magnesium sulphate the next morning. When the bowels have moved, thymol in three doses of 30 grains each is given at hour intervals. At midday another dose of magnesium sulphate is given to remove excess of thymol and lessen the danger of poisoning. No food is permitted until after the thymol treatment is completed. At bedtime emetine bismuthous iodide powder is given for ten consecutive days: 1 grain the first night, 2 grains the second, thereafter 3 grains until a total of 33 grains have

been taken. During the fortnight following the thymol treatment high lavage of the colon is performed on alternate mornings with a solution of quinine in water. After the course of emetine treatment the stools were examined daily for at least three weeks; if the findings were negative, monthly examinations were made for four months. Relapses were treated in the same manner. In only a few cases was a third treatment necessary. Cases which did not respond to this treatment, were considered as practically incurable.

PEDIATRICS

UNDER THE CHARGE OF
THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Acidified Whole Milk as a Routine Infant Food.—MARRIOTT and DAVIDSON (*Jour. Am. Med. Assn.*, 1923, **81**, 2007) give the method of preparing this modification of cow's milk. A good grade of cow's milk is first sterilized by boiling for five minutes. The milk is then cooled and the scum removed. When thoroughly cooled, lactic acid is dropped in slowly, while the milk is gently stirred. Lactic acid (U.S.P.) is used and the amount required is 1 dram to each pint of milk. This is added a drop at a time from a medicine dropper. If the milk is warm when the lactic acid is added, or if the acid is run in too rapidly, large lumps of curds will separate. When properly prepared a smooth, homogenous preparation should result. The concentration of acid is the same as that occurring in ordinary buttermilk and the taste and general physical properties are much the same. In using lactic acid milk for infant feeding dilution is usually not necessary, as the amount an infant would ordinarily take at a feeding is not in excess of the digestive capacity. Carbohydrate should be added to lactic acid milk, as the amount of sugar present is insufficient for the needs of the average infant. The authors recommend commercial corn syrup sold under the name of Karo. This syrup contains a relatively high amount of the difficultly fermentable dextrin, and can consequently be added to the lactic acid milk in large amounts without the danger of producing diarrhea. The amount of syrup usually added to the day's feedings is 1 ounce for infants up to two weeks of age, and from $1\frac{1}{2}$ to 2 ounces for the older infants. In preparing the formulas, the syrup is stirred into the lactic acid milk until it is thoroughly mixed. In cold weather the syrup may be mixed with an equal volume of warm water to facilitate the mixing. Of 142 infants fed in this way, 78 or 55 per cent were suffering from infections during the period of observation. These included otitis media, pneumonia, pyelitis, meningitis, pulmonary tuberculosis, bacillary dysentery, and osteomyelitis. Included in this series were also cases of congenital syphilis, pyloric stenosis, congenital malformations of the heart and spina bifida. These are the usual run of cases seen in the infant ward of any large hospital. The ages of the infants varied from two days to one year. A large proportion of the infants were underweight. Six premature infants are

included in this series. More than half of the babies were under three months of age. The number of days that the formulas were fed varied seven to one hundred and twenty. The average was twenty-two days. The average number of calories fed was 153 per kilogram of body weight. Seventeen of the infants received more than 200 calories per kilogram of body weight. For the entire series the average daily gain in weight was 28 gm. Gain in weight is not the only criterion of the suitability of the diet. The infants in this series rarely developed diarrhea or vomiting. None died as the result of gastro-intestinal disturbance attributable to overfeeding. The mortality of the athreptic infants in the hospital has fallen from 78 per cent in 1919 to 26 per cent during the past year.

Recurring Cardiac Infections in Children with Chronic Valvular Disease.—Smith and Stulik (*Am. Jour. Dis. Child.*, 1923, **26**, 396) observed 80 children during a period of three years. Twenty-one or 26 per cent had frequent periods of slight fever ranging from 99.2° to 100.4° F. In 16 of these, the diagnosis of an active cardiac infection was made. In 7 cases, the diagnosis was based on the finding of a conduction defect of the auriculo-ventricular bundle. Two had premature contractions during periods of fever, one of whom later had definite cardiac dilatation. In the remaining 7, the conclusions concerning the presence of a cardiac infection were based on definite changes in the physical findings of the heart, such as the appearance of a new murmur, a pericardial rub or demonstrable cardiac dilatation. The rate of progression of the cardiac disease was much more rapid and the incidence of severely damaged hearts far greater in the 21 children with recurring periods of temperature than in the remaining 59. The diagnosis of active cardiac infection in children with chronic valvular disease may be difficult, and several weeks may elapse before definite manifestations appear. The electrocardiograph may enable a diagnosis being made earlier in the course of the infection. It was pointed out that one of the difficult problems of the physician in treating children with chronic valvular disease is preventing the condition from progressing. It was suggested that the difficulty might in a measure be overcome by the education of the public, the early elimination of all possible oral and nasopharyngeal infections, and the establishment of convalescent homes.

Chronic Ulcerative Colitis in Childhood.—Helmholz (*Am. Jour. Dis. Child.*, 1923, **26**, 418) reports 5 cases. He comments that, so far as is known, there is no definite etiological factor in this condition. It may be the result of a variety of infections, pyogenic, dysenteric, amœbic, or tuberculous; but wherever a specific cause can be demonstrated, the condition is usually not chronic ulcerative colitis. In none of the cases reported was it possible to demonstrate the presence of any of these infections. In only 2 cases were there other cases of dysentery in the community, and in these two epidemics, all other patients recovered uneventfully in the course of a few weeks. In 1 case the patient had his first attack following scarlet fever complicated by otitis media. In 4 of the 5 cases, the colitis started acutely with a bloody diarrhea. In only one instance was the condition chronic and without diarrhea. The onset was so lacking in symptoms that the small

amount of bloody mucus that the mother noticed on the underclothing was interpreted as the beginning of menstruation. When it continued for a few weeks medical advice was sought. In spite of the treatment the girl became gradually worse. Dysentery did not develop until several weeks later, following an acute bronchopneumonia. As was seen in 1 case the ulceration begins in the lower portion of the bowel, and in the course of the illness the entire colon is involved. In 2 cases that came to necropsy there were ulcerations in the ileum, but this involvement is rare. On proctoscopical examination, the ulcers are usually most marked in the rectum and lower sigmoid, and in the early cases become less numerous in the sigmoid. The colon is usually thickened, the surface appearing red and glazed, with numerous small ulcers. In the severe cases, only small islands of mucosa are left, the entire surface being ulcerated, and presenting a granular appearance. The roentgenogram is characterized by marked narrowing and absence of haustrations in the full extent of the involved colon. The connective tissue found in the inner muscular layer may account for these changes. In 4 of the 5 cases, this picture was very definite. In the fourth it was impossible to make a roentgenogram of the colon, because of the acutely tender condition of the rectum. The stools were usually from five to ten in number, containing a considerable amount of mucopus and blood, frequently in clots. The passing of blood in clots not intimately mingled with mucus is rather characteristic. Two of the 4 patients had good appetites. There was no harmful after-effect of the eating. The other 3 patients had to be coaxed to eat. Each had considerable tenesmus and cramp-like pains in the abdomen, which may have accounted for the lack of appetite. If there were no complications, the patients were usually free from fever. One patient was a febrile during the entire stay in the hospital. The diagnosis is based on the mucopus, associated with the passage of considerable amount of blood, usually in clots. There is a persistence of the dysentery in spite of all medical treatment, and an absence of any of the usual etiological factors. The prognosis is bad under medical treatment. Surgical measures such as colostomy, ileostomy, appendecostomy are helpful, with the after-treatment of continuous irrigation through the surgical opening.

Relative Immunity of Infants under Five Months of Age to Infection with Measles.—HERRMAN (*New York State Jour. Med.*, 1923, **23**, 404) says that infants under two months of age, whose mothers have had measles are immune. The immunity becomes less marked as they grow older, but even at four or five months of age only 25 per cent are infected. From that time the relative immunity quickly diminishes, so that infants over nine months of age are as susceptible as older children. Artificially fed as well as breast-fed babies enjoy this immunity, with a slight difference in favor the breast-fed infants. This relative immunity during the first months of life also manifests itself in other ways. When young infants are infected with measles, the incubation period may be longer, the fever and constitutional symptoms may be less marked, and the eruption, the catarrhal symptoms and buccal manifestations may be less distinct. The immune substances are probably chiefly conveyed to the fetus through the placental circulation. There is no substantial evidence that any important part of the immunity is due to the ingestion of breast milk.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF
JOHN H. STOKES, M.D.,
MAYO CLINIC, ROCHESTER, MINN.

Marital Syphilis.—STRANDBERG (*Acta Dermat.*, 1922, **3**, 546), from a study of 250 marital partners with syphilis, finds the outlook in the marriage of patients with syphilis distinctly discouraging. In only 27.6 per cent did the marital partner escape some consequences of the disease. The transmission of the disease to a healthy partner can take place more than five years after infection in about 20 per cent of the cases and in 2 cases transmission took place after eight years. Syphilitic children can be born as long as ten to fifteen years after the infection of the mother. Manifestations of syphilis may be present in the child at birth even though the mother's infection be three or four years old. In more than 10 per cent of cases a negative blood-Wassermann reaction was obtained from the mothers of syphilitic children. Even the best of treatment during pregnancy may fail to protect the unborn child from infection *in utero*, though the general value of antenatal treatment is conceded. A case is mentioned in which a woman with an active syphilitic infection at her first pregnancy, and practically no treatment, gave birth to a child which has been healthy for many years; but at her second pregnancy, when she was treated with considerable thoroughness, she gave birth to a still-born syphilitic infant. Prolonged observation of children born under suspicion of syphilis is urged.

Acute Disseminate Erythematous Lupus.—VAN DER VALK (*Acta Dermat.*, 1922, **3**, 63) comments on a series of cases of acute disseminate erythematous lupus, the grave and usually ultimately fatal constitutional form of the disease, originating in a previous chronic erythematous lupus or appearing without warning. The polymorphism of the eruptive manifestations, with eczematous, erythematous, vesicular, erosive, bullous, pustular, lichenoid and purpuric lesions in contrast to the uniform picture of the chronic type, is emphasized. The frequency of the mistaken diagnosis of erysipelas and the association with pneumonia and uremia should be especially recalled. The writer reviews the etiological conception in this dermatological riddle, referring especially to the contributions of Jadassohn and Barber to the streptococcal factor in the etiology and of Bloch and Fuchs to the tuberculous factor. He mentions the theories of Kreibich and Gennerich, who believe the disease to be the result of toxins elaborated by the lymph nodes under some pathological stimulus. EHRMANN and FALKENSTEIN (*Arch. f. Dermat. u. Syph.*, 1922, **141**, 408), in an elaborate study of a series of 130 cases with autopsy, state, with striking definiteness, their conclusion that erythematous lupus, as they have seen it, occurs in tuberculous individuals in 98 per cent of cases, and is due to tubercle bacilli carried to the skin presumably from the lymph

glands. They consider that acute disseminate erythematous lupus is a tubercle septicemia and that a recent focus of tuberculosis can be found in all these cases.

Arsphenamine in Treatment of Syphilis.—MILLS (*Brit. Jour. Dermat.*, 1923, **35**, 131), in discussing the arsphenamine treatment of syphilis, states that in the use of sulpharsenol (sulpharsphenamine) he has experienced very little difficulty with local reaction and finds the drug when given intramuscularly much more rapidly spirillicidal than when given intravenously. In discussing the merits of "606" as compared with "914" (neo-arsphenamine) he unhesitatingly gives the preference to "606" as the more effective therapeutically, even inequivalent dosage, probably, he thinks, because of its slower elimination. He comments on the instability and lack of uniformity of neo-arsphenamine and the inadequacy of therapeutic testing as compared with that enforced in Great Britain in the case of arsphenamine.

Treatment of Dermatitis Venenata.—STRICKLER (*Jour. Am. Med. Assn.*, 1923, **80**, 1588) reports upon the use of antigen or toxin for the treatment of dermatitis venenata by desensitization. The preparation of this toxin from plants of the Rhus family was previously described (*Jour. Am. Med. Assn.*, 1921, **77**, 910). Three to 5 intramuscular injections of this specific antigen were given, the dose ranging from 0.3 to 0.5 cc, although doses up to 0.7 may be given. The first 2 doses are given at two-hour intervals, the remainder at intervals of forty-eight to seventy-two hours, depending upon the response. Marked improvement within twenty-four hours usually occurs, and the skin returns to normal within four or five days. Nearly 95 per cent of 356 patients were markedly improved by this treatment, and the results were vastly superior to the local applications usually used. The process is essentially a desensitization and it is hoped that a larger series in highly susceptible cases will indicate its value as a cure for hypersusceptibility as well as a treatment measure.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

The Treatment of Patients Pregnant and Tuberculous.—Before a recent meeting of the Association of Obstetricians and Gynecologists, using the French language, THELIN (*Gynec. et obstét.*, 1923, **3**, 283) contributed a paper upon this subject. His studies were made in the Maternity Hospital at Lausanne, and the great majority of the patients were in early gestation. In 90 cases the question as to the interruption of pregnancy was considered; in 41 pregnancy was interrupted

and nothing more was done. In other patients 8 sterilizations were performed by excising or ligating the tubes, 1 case aborted and 1 case was afterward studied during and after labor. The indication which seemed to justify the interruption of pregnancy was the fact that the patient's condition became greatly aggravated after pregnancy occurred. The 41 cases in which pregnancy was interrupted are divided into the first group, 9 in number, where the cervix was dilated by a laminaria tent, the ovum was removed by the finger and in a few cases a curette was used in addition. The results were immediately good, 2 patients could not be traced; 4 died of tuberculosis within a year, 3 of the women survived. One of these had again become pregnant and given birth to a healthy child, a second had tuberculosis of the larynx and it was thought best to again interrupt the pregnancy. In the third patient the interruption was practised in 1912, and the patient's condition was complicated by cardiac weakness. Since 1912, 4 pregnancies had occurred, 2 terminated by spontaneous abortion and 2 by the artificial interruption of pregnancy. In the second group, with 6 cases, where pregnancy was interrupted and then the abdomen opened and the Fallopian tubes resected, all recovered from the operation; 1 died three months afterward from tuberculosis and 5 still survive. In the third group, 27 cases, pregnancy was interrupted by incising and emptying the uterus and sterilization was performed by removing the Fallopian tubes. Of the 27, 19 were in comfortable health and able to care for a family or to do active work, 3 could not be traced; 5 had died, 3 of tuberculosis and 2 of influenza. In all, 36 patients had been treated by removing the Fallopian tubes, and in these menstruation had remained regular, the uterus continued to be normal in size and the general health of the patients had been remarkably good.

Vasomotor Tone during Pregnancy.—Louros (*Zentralbl. f. Gynäk.*, 1923, **43**, 1667) contributes a paper upon this subject, in which he calls attention to the state of the vasomotor nerves as a symptom of pregnancy. His experiments were made by injecting adrenalin after taking the pulse and blood-pressure with the Riva-Rocci apparatus. Observations were made at intervals of three minutes. In the case of an individual in a normal condition there occurred a gradual rise of blood-pressure which reached its maximum in about fifteen minutes. This was followed by a gradual descent, lasting about fifteen minutes. When, however, there was an increased sensibility in the sympathetic or parasympathetic system, and adrenalin was given, there was a very marked rise in pressure, followed by a great and immediate drop. When there was primary irritability of the parasympathetic system, and adrenalin was injected, the blood-pressure rose very little or, instead of rising, showed signs of sinking. This phenomenon occupied about ten minutes. After this method, experiments were made upon pregnant women at each month of gestation and also of women in labor and who had been delivered. Thirty-eight patients were examined and in none of these was the condition of vasomotor tension found to be normal. In 32 there was the condition called parasympathetic or vagotone, and in 6 there was little or no reaction, indicating an abnormal condition of the sympathetic system. The 32 patients

did not describe symptoms which especially drew attention to the condition. One complained of excessive perspiration; variations of the pulse-rate were present; in some abnormalities in the pigmentation of the skin were also observed. These abnormalities disappeared at the termination of pregnancy. In the 6 women who had the condition known as sympathetic sensibility, there was a very considerable rise in pressure after the injection of adrenalin. This was followed by rapid descent. Most of these patients showed irregular action of the heart, difficulty in respiration, heart murmurs and other symptoms of undue sensibility. In 1 of these patients, after the pregnancy terminated, the same symptoms persisted for some time. The writer also adds to his paper the adrenalin blood-pressure curve of 22 eclamptics. In 17 of these, five minutes after adrenalin was injected, the blood-pressure, which previously had been high, sank rapidly, free perspiration was also present and in 14 there was positive evidence of implication of the endothelia of the vessels. In 6 patients there were symptoms of hyperthyroidism. The writer concludes from these observations that during pregnancy there is a condition of the vasomotor nerves which indicates a parasympathetic state. This serves to mask and compensate for many disturbances during pregnancy. In toxemic patients with eclampsia this condition is very greatly exaggerated. While we do not know the exact cause of this, it undoubtedly has to do with the condition known as toxemia of gestation.

Hydatidiform Mole and Chorio-epithelioma.—Gordon (*Surg., Gynec. and Obst.*, 1923, **36**, 242) at the Bellevue Hospital, finds that in 4500 abortions there were discovered 21 hydatidiform moles, a percentage of 0.4, other cases may have been overlooked. The mortality of this series was 9 per cent and this was from a low grade of sepsis following moderate but prolonged bleeding. In the Laboratory of the Bellevue Hospital in 8000 autopsies and with the examination of more than 3500 surgical specimens, there has been identified but one chorio-epithelioma, and this was a metastatic growth of the vulva and was considered as doubtful. Probably chorio-epithelioma does not occur more frequently than a fraction of 1 per cent. Statistics vary as to the frequency in which chorio-epithelioma follows hydatidiform mole. In the writer's experience it is rare. So far as treatment is concerned, the writer urges the substitution of abdominal hysterotomy for curetting and other methods formerly advised. If the condition of the cervix permits, the uterus may be thoroughly explored by the fingers, and the abnormal tissues may safely be removed with little danger. The uterus can then be palpated and its interior carefully studied and if there be found a soft and friable area in the myometrium, hysterectomy is advisable. If the uterus be manually emptied and allowed to remain, these patients should be kept under observation and hysterectomy be performed should hemorrhage return. Unless the fingers can readily gain access to the uterus and examine its cavity, abdominal section with incision into the uterus and thorough examination is indicated. By this method pathological tissues in the uterus can be safely removed and the uterus saved. If on performing section there is undoubted evidence of chorio-epithelioma, hysterectomy is indicated. Not only changes in the uterus but in some cases extensive thrombosis of the pelvic veins are signs of

this malignant condition. Theoretically the use of radium or deep roentgen-ray treatment should be of advantage but there is no record of the trial and results of this method. In from 80 to 90 per cent of cases bilateral ovarian cystomata are present. As a rule these growths are short lived and probably arise from distention and overgrowth of corpora lutea, they usually disappear spontaneously after the abnormal condition of the uterus is remedied. Hydatidiform degeneration of the chorion, the writer believes is infrequent, and actual chorio-epithelioma from his observation is extremely rare. The relative malignancy of a given growth can be accurately distinguished by microscopical examination only. The methods already described by the writer are urged and curetting is considered dangerous and practically worthless as a means of diagnosis.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Intracervical Enucleation.—LAHEY (*Ann. Surg.*, 1923, **78**, 61) directs attention to this method of intracervical enucleation for removal of the cervix in hysterectomy for benign lesions, because in his hands it has proven such a rapid, safe and satisfactory measure for the accomplishment of this purpose. It consists in the routine supracervical hysterectomy as done, for example, for fibroid uterus up to the point of section of the cervix. At this point the cervix is not cut across or even removed by wedge-shaped excision, but is cored out by vertical-circular incisions placed just within the outermost boundary of the cervix. The cervix is pulled up with each circular incision, until as the last incision reaches the vagina the thin remaining shell of cervical tissue is inverted from below upward, to drop back as the last circular incision separates the cervical plug from its shell of remaining cervical tissue. This leaves an opening through which a small strip may be tucked into the vagina to prevent the possible return of infected vaginal contents. The stumps of the round, and if need be the broad, ligaments fit easily into the large aperture and may be sutured securely there. It is usually necessary to place a large mattress stitch through the entire cervical shell to control the oozing which occurs from the walls from the remaining shell. Lahey has used this method of getting rid of the cervix in hysterectomy for benign lesions to overcome the postoperative leucorrhea without producing the vaginal shortening which results from the employment of complete hysterectomy. The disadvantages of the procedure have

been, first, the excessive oozing from the cervix during the process of coring, resulting often in a pooling of blood at the bottom of the pelvis and producing a somewhat messy condition at this stage of the procedure. This may be overcome in some measure by folding a towel into a triangular shape and introducing the apex into the fossa of Douglas, so that any ooze is caught in the hollow of the towel so placed. This oozing has been immediately controlled as soon as the cervical mattress suture has been tied. The operation is but little prolonged, there is no danger to the ureters and excellent support can be obtained by the fixation of the round and broad ligaments as deeply as desired in the remaining cervical aperture.

Value of Cervical Surgery.—No part of the female genitalia has received so much attention in recent years as the cervix uteri. Endless papers and monographs have been written upon the remote effects of the lacerated and infected cervix. For this reason it seemed to POLAK (*Am. Jour. Obst. and Gynec.*, 1923, **5**, 640) that it might be well to determine what constitutes the surgical cervix and how much pathology must exist before we are justified in subjecting the patient to excision, trachelorrhaphy, tracheloplasty or amputation. Therefore, he has reviewed the records of 350 operations upon the cervix, analyzed the indications for the procedures and the end-results as to the effect on sterility, discharge, pregnancy and labor. Critical study of this series shows that operation on the surgical cervix, *i. e.*, for extensive or multiple lacerations, extensive erosion with hyperplasia or cystic degeneration, even when the type of operation is carefully selected, in a large number of cases does not cure the leucorrhea or sterility, and that unless the operation is preceded by a long period of preliminary local treatment the leucorrhea is cured in only a little more than 50 per cent of the cases operated upon. It is therefore urged that all operations on chronically infected cervices be preceded by local treatment. Only a relatively small number of sterilities are cured by operations on the cervix, and these should only be done for this cause after a Hühner and a Rubin test have shown that the fault is in the biochemical changes in the cervical discharge. After amputation or excision should pregnancy occur it is more likely to terminate in abortion than has been the case when trachelorrhaphy has been selected. Dystocia during labor is also more common after amputation and excision than after cervical repair.

Hysteropexy for Prolapse of the Uterus.—In recommending the performance of hysteropexy in the treatment of uterine prolapse, MAXWELL (*China Med. Jour.*, 1923, **37**, 393) is aware that this operation is supposed to be unsafe, owing to the possibility of intestinal obstruction following on the stretching of adhesions, a band being left between the uterus and the point of fixation. Of 45 patients on whom he had performed this operation all were alive except 2, who died from diseases having no relation to the uterine trouble. In answer to the statement that hysteropexy interferes with the expansion of the uterus in the event of a subsequent pregnancy, the author states that there have been 20 pregnancies subsequent to operation in his series, all of which were normal. He believes that the bad name which hysteropexy has

acquired is due in large part to the poor technic which has been employed. A number of operators have placed their sutures in the fundus of the uterus, some even anteverting the organ by a suture passed through the top of the posterior wall. Some operators leave non-absorbable sutures permanently uniting the uterus to the abdominal wall. In the former procedure (anteverting the uterus), if the attachment to the abdominal wall holds it is quite evident that by no possibility can the uterus enlarge normally, but must do so at the expense of the posterior wall alone, with the risk of rupture of the uterus or malpresentation. In the second procedure any buried permanent sutures are likely to affect the regular expansion of the uterus and entail the same risks as in the former case. While no operation for prolapse has proven perfectly effective in all cases, the author believes that hysteropexy will permanently cure the bulk of patients and relieve a considerable proportion of the rest. Of 39 cases which he has been able to follow closely there have been recurrences in 5, which means a successful result in 87 per cent. Of the recurrences 2 recurred after childbirth, 1 recurred due to increased intra-abdominal pressure due to a rapid splenic enlargement, while the other 2 cases recurred for no reason that could be discovered.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH; PITTSBURGH, PA.

The Complement-fixation Reaction as Applied to Leprosy.—Many have endeavored to use the reaction of complement-fixation as a means of increasing our knowledge of leprosy, either in making a certain diagnosis or to determine an etiological relationship to the disease. In no instance have these efforts to apply complement-fixation been eminently successful. By utilizing many facts and ideas evolved from an extensive experience with complement-fixation in tuberculosis, LEWIS and ARONSON (*Jour. Exper. Med.*, 1923, **38**, 219) developed a new method for testing 45 specimens of sera obtained from 39 cases of leprosy. The antigens employed were many and consisted of bacillary emulsions of B. lepræ (Clegg), B. lepræ (Duval), B. lepræ (Kedrosky), B. smegmatis, timothy hay bacillus, Must bacillus, etc.; as well as alcoholic extract of bovine B. tuberculosis and B. lepræ (Clegg), Petroff's antigen and cholesterol and acetone antigens of human heart. The test was performed by adding to 0.1 cc of the serum antigen, 2 units of complement and sufficient salt solution to bring the total volume to 1 cc. After incubation for two hours at 37° C. 4 units of anti-sheep amboceptor

and 0.1 cc of a 5 per cent suspension of sheep cells were added. After thirty minutes incubation in the water bath and again, after overnight in the ice-box, the results were noted. After various experiments, it was found that the blood serum of cases of leprosy exhibited the ability to fix complement with a wide variety of antigens including to a greater or less extent those derived from any of the acid-fast group of bacteria available to the authors. Control sera from normal individuals, from cases of tuberculosis, or from cases of syphilis entirely failed to react with certain antigens, whereas serum from cases of leprosy so reacted to the extent of over 93 per cent. The most characteristic fixation given by the leprosy sera was that with B. lepræ (Clegg) used as antigen, either in the form of a bacterial emulsion or of an alcoholic extract of the dried culture. Antibody absorption could be demonstrated in the acid-fast group if the absorbing bacteria were removed by filtration. Otherwise the resulting fluid was strongly anti-complementary. Leper serum was not deprived of the complement-fixing body when so treated with either B. tuberculosis or B. lepræ (Clegg.)

A Study of Rabbit Spirochetosis.—Since 1912, several investigators have noted the occurrence in rabbits of a spontaneous venereal spirochetosis resembling syphilis, in the lesions of which a spirochete, very similar in appearance to *Treponema pallidum* and named *Treponema cuniculi* by Noguchi, has been demonstrated. As a result the value of all the experimental work on rabbit syphilis is challenged. Realizing the importance for more extensive studies at this time, WARTHIN, BUFFINGTON and WANSTROM (*Jour. Infect. Dis.*, 1923, **32**, 315) reported their findings in a detailed investigation of the cuniculi disease, basing the study on the disease as produced experimentally in 18 rabbits which were inoculated by scarification from a spontaneous case found in a Western rabbit. The lesion, so produced, was a superficial one, papillomatous or condylomatous in character, limited to mucous membranes or skin, which spread by contiguity, continuity or autoinoculation and could be transmitted by inoculation, contact and coitus. The lesions were essentially epithelial and not vascular, being confined to the epithelial surface and upper portion of the subepithelial tissues, with marked hyperplasia of the epithelium and papillary layer. Histologically, the spirochetosis did not suggest chancre. No evidence of systemic infection was found and no lesions containing spirochetes occurred in any of the internal organs. The incubation period varied from 5 to 56 days, averaging 23.81 days for 16 inoculations. The general health of the infected animals remained good save in the event of intercurrent infections. The Wassermann reaction was negative and no general immunity was developed. From the lesions the spirochetes could readily be obtained by cover-glass smears of the surface or by scarification and could be best demonstrated by the WARTHIN-STARRY silver-agar method for cover-glass smears (*vide Jour. Infect. Dis.*, 1922, **30**, 592). The organisms resembled some of the mouth spirochetes more closely than *Treponema pallida*, than which they were usually thicker and larger, as well as softer and more flexible, tending to form circles, V and Y shapes and twisted stellate forms. In sections of tissue lesions, the cuniculi lay in entangled masses on and in the epithelium, and just below it, rarely penetrating in any appreciable numbers deeply into

the tissues. The authors indicate that cuniculi spirochetosis does not resemble syphilis in its clinical course or in its local or general pathological picture and should not be called "rabbit syphilis." Moreover, they say that the spontaneous rabbit disease can be easily differentiated from pallida infections by its morphology, as shown in a silver-agar cover-glass smears and by the pathology of the lesions. They believe, however, that it will be necessary to repeat much of the experimental work in this new light, inasmuch as "too many important deductions have been made from rabbit experimental work to admit of any doubt being allowed to remain as to their accuracy."

HYGIENE AND PUBLIC HEALTH

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MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Studies on Pneumococcus Immunity. II. Active Immunization of Monkeys with the Homologous Pneumococcus Vaccine.—CECIL and STEFFEN (*Jour. Exp. Med.*, 1923, **38**, 149) state that three subcutaneous injections of Pneumococcus Type II vaccine confer on monkeys a complete immunity against experimental Pneumococcus Type II pneumonia. A similar protection can be bestowed on monkeys against Pneumococcus Type IV pneumonia by three subcutaneous injections of a vaccine prepared from the same strain of pneumococcus. The subcutaneous injection of monkeys with three doses of Pneumococcus Type III vaccine confers a complete immunity against this type in only 50 per cent of cases (4 out of 8 monkeys vaccinated). In spite of the immunity induced in monkeys by three subcutaneous injections of Pneumococcus Types II, III and IV vaccine, specific protective bodies against the homologous types are not demonstrable in their serums when the vaccine is so administered.

Schick Tests and Immunization Against Diphtheria in the Eighth Sanitary District of Vermont.—KIDDER (*Public Health Reports*, 1923, **38**, 663) gives the following conclusions: (1) That both the percentage of susceptibles and the degree of susceptibility to diphtheria are higher in sparsely populated sections than in thickly settled or urban communities. (2) That the percentage of susceptibles among rural people, without regard to class or environment, is higher than that of the well-to-do classes in cities. (3) That in the rural districts, as well as in the cities, the percentage of susceptibles is much higher among the well-to-do than among the poorer classes. (4) That the percentage of suscep-

tibles is much higher among the native born than among the foreign born. (5) That age is a relatively unimportant factor in the immunization of individuals living in strictly rural communities. This conclusion is supported by the fact that of 87 teachers between the ages of twenty and sixty years, included in the group of 2030 persons tested, 82 per cent gave positive Schick reactions. It was found also that the degree of susceptibility as evidenced by Schick reactions was as high among the susceptible adults as among the susceptible school children. (6) That the higher the degree of susceptibility the less reaction there is to toxin-antitoxin. (7) That those individuals having a positive combined Schick reaction are more likely to have a severe reaction from toxin-antitoxin. (8) That notwithstanding the distances to be covered and the other factors in the relatively high cost and difficulties of such work in rural districts, the use of the Schick test and of toxin-antitoxin for immunization against diphtheria is, in view of the extent and degree of susceptibility to the disease and the frequent lack of facilities for prompt and adequate treatment of cases, especially important in rural communities and should be included at appropriate times in the program of activities of rural health departments.

Changes in a Small Town Brought About by the Health Department.—BAGBY (*Public Health Reports*, 1923, **38**, 456) contrasts medical practice of 1909 with that of 1922, and draws attention to the difference, due to public health measures. Malaria, typhoid fever, hookworm infestations and intestinal diseases have largely disappeared. Improved milk supply, satisfactory water and sewage systems, drainage against malaria and improved housing conditions account for the improvement.

A Bacteriological Study of Vulvo-vaginitis of Children.—ANDERSON, SCHULTZ and STEIN (*Jour. Infect. Dis.*, 1923, **32**, 444) found that in a series of 42 cases of vulvo-vaginitis among children reporting to a dispensary clinic for treatment, 37.5 per cent were due to the gonococcus and 64.3 per cent were non-specific. In 53.3 per cent of the specific cases, the gonococcus was isolated in pure culture. In the remainder, the specific diagnosis was based on the presence within leukocytes of morphologically typical, Gram-negative diplococci. Although the newer cultural methods have simplified the isolation of the gonococcus, the direct smear examination should be given preference over the cultural method as a diagnostic procedure. In no case was it possible to cultivate the gonococcus when gonococcus-like bacteria were not detected in the smear examination. It was impossible, by immunological methods, to differentiate the gonococci isolated from children from those derived from women. In the non-gonorrheal cases a mixed flora was present, but streptococci of intestinal origin appeared to be the most important agents. Staphylococci, colon bacilli and Gram-positive bacilli were frequently encountered, probably as secondary invaders or harmless symbionts. Uncleanliness and local irritation are believed to be an important, and probably the primary, factor in the non-specific cases, the condition thus established being maintained or made worse by bacterial localization. In the latter part of the process, bacteria of intestinal origin appear to be most important. Cases in which

filth and irritation appeared to be the chief factors yielded most readily to the routine therapeutic procedures which were applied in all cases. The gonorrheal cases were most stubborn. In an intermediate position, as regards the readiness with which they yielded to treatment, were the cases in which local irritation was followed by the localization of bacteria other than the gonococcus. Quarantine and exclusion from school are not believed to be necessary in the non-gonorrheal cases.

Further Notes upon Experimental Measles in Rabbits and Monkeys.—NEVIN and BITTMAN (*Jour. Infect. Dis.*, 1923, **32**, 33) passed the virus of measles obtained from patients on the second day of the disease through 4 rabbits and then produced symptoms typical of measles in a monkey. In a second series the virus was passed through 3 rabbits and then through 3 monkeys in which symptoms typical of measles were produced. The monkey-to-monkey passage eliminated any question of rash due to foreign protein. A control monkey injected with normal human blood showed no reaction. The authors state that the results of these two series of passages confirm their previous findings that the virus of measles survives rabbit passage and produces symptoms typical of measles in the monkey (M. rhesus).

The Devil's Grip in Virginia.—ARMSTRONG (*Pub. Health Rep.*, 1923, **38**, 1964) reports an epidemic in which the outstanding features are: Patients usually children, often several in a home; onset sudden, with acute pain, generally of the epigastrium, later shifting to one side of the chest; shallow, painful, rapid respiration; temperature, 101° to 103° F.; often symptoms variable, and all transitory, usually subsiding in twelve to thirty-six hours. Physical examination negative. This was considered to be identical with the disease described by Dabney in 1888.

Does Commercial Pasteurization Destroy Tubercle Bacilli in Milk.—BARTLETT (*Am. Jour. Public Health*, 1923, **8**, 807) conducted experiments to determine whether commercial pasteurization renders milk safe from the standpoint of tuberculosis and found that pasteurization by the holding method between 142° F. and 148° F. for thirty minutes destroys the tubercle bacillus in milk. Specimens of raw milk taken from mixing vats holding from 300 to 1200 quarts each showed the presence of tubercle bacilli by guinea-pig inoculation in 50 per cent (44 per cent). The relative frequency with which tubercle bacilli were found was greater in milk from the larger mixing vats than in that from the smaller mixing vats.

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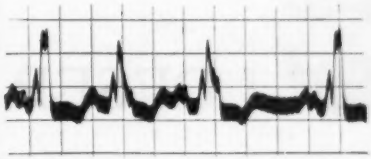

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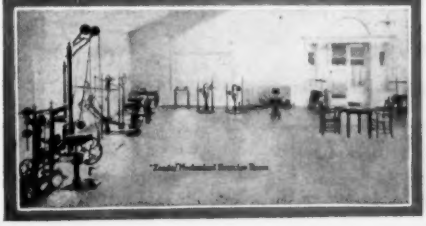

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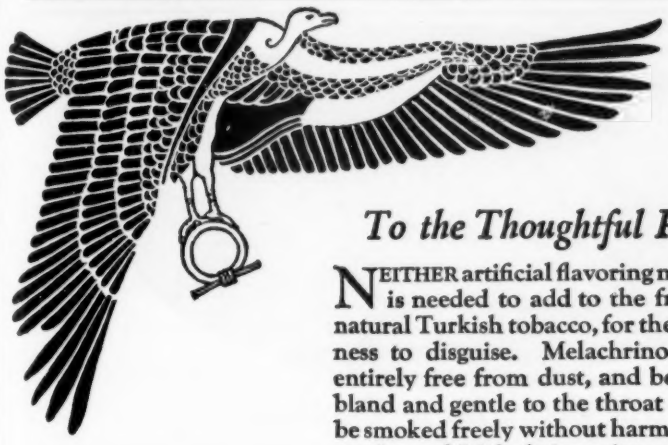

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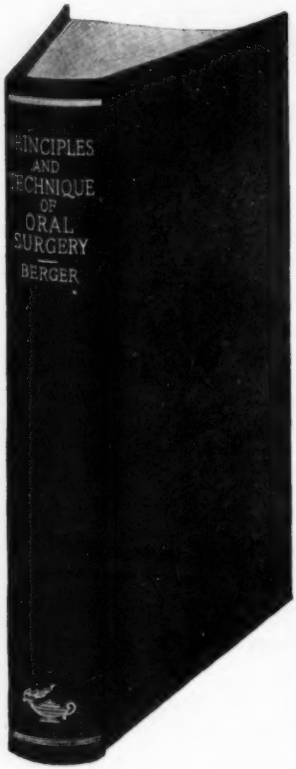

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Merck & Co. 16
Sanborn Company ....
Arthur H. Thomas Co. 3
Wilmot Castle Co. 7

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Sanborn Company ....
Arthur H. Thomas Co. 3

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Katherine L. Storm, M.D. 21

Blood Pressure Apparatus

W. A. Baum Co. ..... 2d Cover
Becton, Dickinson & Co. 36

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Abbott Laboratories 18
Arlington Chemical Co. 15
Armour & Co. 13
E. Bilhuber, Inc. 14
Calco Chemical Co. 5
G. W. Carnrick Co. 11
Ciba Co. ..... 4th Cover
Fairchild Bros. & Foster 5
Hoffmann-LaRoche Chemical Works ... 6
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Maltbie Chemical Co. 21
Merck & Co. 16
H. A. Metz Laboratories 24
H. K. Mulford Co. 15
National Aniline & Chemical Co. 18
New York Intravenous Laboratory 22
Parke, Davis & Co. 29
Riedel & Co. 21
Schering & Glatz, Inc. 19
Sharp & Dohme 4
F. A. Upsher Smith 9
Smith, Kline & French 24
Winthrop Chemical Co. 26

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Electrocardiographs

Cambridge & Paul Instr. Co. 21

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Borcherdt Malt Extract Co. ..... 3d Cover
Celestin's Vichy 6
Chicago Dietetic Supply House 28
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Laboratory Products Co. 8
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Cheplin Biological Laboratories 4
Lederle Antitoxin Laboratories 20

Malt Sugar

Borcherdt Malt Extract Co. ..... 3d Cover

Radium

Radium Emanation Corp. ..... 3d Cover

Resorts and Hotels

Battle Creek Sanitarium 28
Glen Springs 25
The Homestead, Hot Springs, Va. 25
The "Spa", Waukesha, Wis. 28

Sutures and Ligatures

Armour & Co. 13
Davis & Geck, Inc. ..... 2d Cover

Syringes, Needles and Thermometers

Becton, Dickinson & Co. 36

X-Ray Apparatus, Tubes, etc.

Victor *X*-Ray Corp. 17

Miscellaneous

Dental Items of Interest Co. 30
Kalak Water Co. 26
Lea & Febiger 31–34
Melachrino Cigarettes 27

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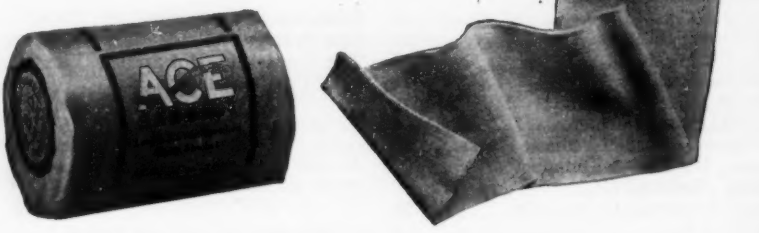

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INDEX

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